

# Mathematical Biophysicists, Theoretical and Molecular Biologists: Their Biographies and Research Areas

Related Topics, Research Areas and  
Concepts

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# Notable Mathematical Biophysicists and Theoretical Biologists

## Nicolas Rashevsky

| Nicolas Rashevsky                                                                                                                                      |                                                     |
|--------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|
|  <p>Nicolas Rashevsky, the Founder of Mathematical Biology in USA</p> |                                                     |
| <b>Born</b>                                                                                                                                            | November 9, 1899<br>Chernigov, Ukraine              |
| <b>Died</b>                                                                                                                                            | January 16, 1972<br>Holland-Michigan, United States |
| <b>Residence</b>                                                                                                                                       | US                                                  |
| <b>Nationality</b>                                                                                                                                     | US and Russian                                      |
| <b>Ethnicity</b>                                                                                                                                       | Russian                                             |
| <b>Fields</b>                                                                                                                                          | Theoretical physics, Mathematical biology           |
| <b>Institutions</b>                                                                                                                                    | University of Chicago, Ann Arbor, Michigan          |
| <b>Alma mater</b>                                                                                                                                      | Kiev University, University of Chicago              |

**Nicolas Rashevsky** (November 9, 1899 – January 16, 1972) was a Ukrainian-American theoretical biologist who pioneered mathematical biology, and is also considered the father of mathematical biophysics and theoretical biology<sup>[1] [2] [3] [4] [5]</sup>.

### Academic career

He studied theoretical physics at the University of Kiev in Russia before 1917, and immigrated first to Turkey, Poland, France, and then to the US in 1924 because of the October revolution. In USA he worked at first for the Westinghouse Research Labs in Pittsburgh where he focused on the theoretical physics modeling of the cell division and the mathematics of cell fission, a subject that was anecdotally said to have attracted fission-related defense interests. He was awarded a Rockefeller Fellowship in 1934 and went to the University of Chicago to take up the appointment of assistant professor in the Department of Physiology. In 1938 he made his first major contribution by publishing the first book on *Mathematical Biophysics*, and then in 1939 he also founded the first mathematical biology international journal entitled *The Bulletin of Mathematical Biophysics* (BMB)<sup>[6]</sup>; these two essential contributions founded the field of mathematical biology, with the BMB journal serving as the focus of contributing mathematical biologists over the last 70 years.

## Major scientific contributions

His later efforts focused on the topology of biological systems, the formulation of fundamental principles in biology, relational biology, set theory and propositional logic formulation of the hierarchical organization of organisms and human societies<sup>[7] [8]</sup>. He also introduced the concept of "organismic sets", that was later developed by other authors<sup>[9]</sup> through applications of category theory to relational biology<sup>[10]</sup>, organismic supercategories and Complex Systems Biology<sup>[11]</sup>. In 1938 he published the first book on mathematical biology and mathematical biophysics entitled: "*Mathematical Biophysics: Physico-Mathematical Foundations of Biology*." This fundamental book was then followed in 1940 by "*Advances and applications of mathematical biology*.", and in 1947 by "*Mathematical theory of human relations*", an approach to a mathematical model of society. In the same year he establishes the World's first PhD program in Mathematical Biology at the University of Chicago. Only J. H. Woodger seems to have preceded in 1937 Rashevsky's efforts in mathematical biology with his genetic axiom system<sup>[12]</sup>. However, Woodger's 'genetical axiom system' has had only very limited impact on the subsequent development of genetics because it is restricted



Professor Nicolas Rashevsky in 1924

to Mendelian genetics; one could similarly comment on Rosen's later papers on quantum genetics that—unlike his other work on complexity and life, categories of metabolic-replication systems, complex dynamics, etc— did not make any apparent impact on either molecular biology or molecular genetics, DNA dynamics, DNA, and so on.

## Rashevsky's most notable students

Some of Rashevsky's most outstanding PhD students who earned their doctorate under his supervision were: George Karreman, Herbert Daniel Landahl, Robert Rosen and Anatol Rapoport. In 1948, Anatol Rapoport took over Rashevsky's course in mathematical biology, so that Rashevsky could teach mathematical sociology instead.

## Administrative and political obstacles

However, his more advanced ideas and abstract relational biology concepts found little support in the beginning amongst practicing experimental or molecular biologists, although current developments in complex systems biology clearly follow in his footsteps. In 1954 the budget for his Committee of Mathematical Biology was drastically cut; however, this was at least in part politically imposed, rather than scientifically, motivated. Thus, the subsequent University of Chicago administration—notably represented by the genetics Nobel laureate George Wells Beadle—who reversed in the 1960s the previous position and quadrupled the financial support for Rashevsky's Committee for Mathematical Biology research activities ("*Reminiscences of Nicolas Rashevsky*." by Robert Rosen, written in late 1972). There was later however a fall out between the retiring Nicolas Rashevsky and the University of Chicago president over the successor to the Chair of the Committee of Mathematical Biology; Nicolas Rashevsky strongly supported Dr. Herbert Landahl-his first PhD student to graduate in Mathematical Biophysics, whereas the president wished to appoint a certain US biostatistician. The result was Rashevsky's move to Ann Arbor, Michigan, and his

taking ownership of the well-funded "*Bulletin of Mathematical Biophysics*".

### **Formation of Mathematical Biology, Inc.**

He also formed in 1969 a non-profit organization , "*Mathematical Biology, Incorporated*", which was to be the precursor of "*The Society for Mathematical Biology*", with the purpose of "*dissemination of information regarding Mathematical Biology*". In his later years, after 1968, he became again very active in relational biology and held, as well as Chaired, in 1970 the first international "*Symposium of Mathematical Biology*" at Toledo, Ohio, in USA with the help of his former PhD student, Dr. Anthony Bartholomay, who has become the Chairman of the first Department of Mathematical Medicine at Ohio University. The meeting was sponsored by *Mathematical Biology, Inc.*

### **Final quest for principles of biology**

Rashevsky was greatly influenced and inspired both by Herbert Spencer's book on the Principles of Biology (1898), and also by J. H. Woodger 'axiomatic (Mendelian) genetics', to launch his own search and quest for biological principles, and also to formulate mathematically precise principles and axioms of biology. He then developed his own highly original approach to address the fundamental question of What is Life? that another theoretical physicist, Erwin Schrödinger, has asked before him and Robert Rosen from the narrower viewpoint of quantum theory in biology. He wished to reach this 'holy grail' of (theoretical/ mathematical) biology, but his heavy work during the late 1960s— in spite of his related health problems— took its toll, and finally prevented him in 1972 to reach his ultimate goal.

### **Biography**

In 1917, Nicolas Rashevsky joins the White Russian Navy and in 1920 he and his wife, Countess Emily had to flee for their lives to Constantinople where he taught at the American College. In 1921 they moved to Prague where he taught both special and general relativity. From Prague, he moved in the 1930s to Paris, France, and then to New York, Pittsburgh and Chicago, USA. His life has been dedicated to the science that he founded, Mathematical Biology, and his wife Emily was very supportive and appreciative of his scientific efforts, accompanying him at the scientific meetings that he either initiated or attended. He cut a tall, impressive figure with a slight Russian accent, but a clear voice and thought to the very day when in 1972 he died from a heart attack caused by coronary heart disease. His generosity was very well known and is often recognized in print by former associates or visitors. As the Chief Editor of BMB he had a declared policy of helping the authors to optimize their presentation of submitted papers, as well as proving many valuable suggestions to the submitting authors. His suggested detailed changes, additions and further developments were like a real 'gold mine' for the submitting authors. He managed to stay aloof of all science 'politics' most of the time, even in very adverse circumstances such as those during the MacCarthy era when completely unfounded political accusations were made about one or two members of his close research group. Not unlike another American theoretical physicist Robert Oppenheimer, he then had much to lose for his loyal support of the wrongly accused researcher in his group.

## Notes and references

This article incorporates material from Nicolas Rashevsky on PlanetMath, which is licensed under the Creative Commons Attribution/Share-Alike License. The article also incorporates additional data from planetphysics.org<sup>[13]</sup>; furthermore, both external entries are original, contributed objects in the public domain.

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- [2] <http://planetphysics.org/encyclopedia/NicolasRashevsky.html> Nicolas Rashevsky's Biography
- [3] <http://www.smb.org/> The Society for Mathematical Biology
- [4] Robert Rosen *Essays on Life* (2004)
- [5] Evelyn Fox Keller *Making Sense of Life* pp. 82-89
- [6] <http://www.springerlink.com/content/x513p402w52w1128/>
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## External links

- Books by Rashevsky (<http://openlibrary.org/a/OL2010564A/Nicolas-Rashevsky>)
- The Bulletin of Mathematical Biophysics (<http://www.springerlink.com/content/x513p402w52w1128/>)
- Rashevsky's theory of **two-factor systems** for neural networks (<http://www.springerlink.com/content/m0358168q574qm11/>)

## See also

- Mathematical biology
- Principles of Biology
- Relational Biology
- Biocybernetics
- Mathematical sociology
- Bulletin of Mathematical Biophysics
- Complex Systems biology
- Theoretical biology
- Mathematical Biophysics
- Bioinformatics
- Society for Mathematical Biology
- The Society for Mathematical Biology (<http://www.smb.org/>)
- Organismic set theory
- Organism
- Organismic sets of zeroth order
- Organismic development
- Organization
- Two-factor theory of nerve impulse
- Mathematical logic
- Topology

- Epigenetic landscape
- Network theory
- Graph theory
- Algebraic topology
- Category theory
- Symbolic logic
- Relation algebra
- Neuron
- Neurophysiology
- Neural networks
- George Karreman
- Robert Rosen
- Conrad Hal Waddington
- Brian Goodwin
- Herbert Spencer
- Brownian motion-theory
- Theoretical physics
- October revolution
- University of Kiev
- Cell division

## D'Arcy Thompson

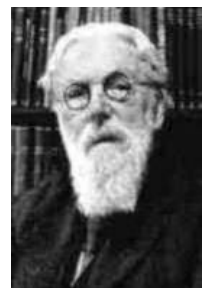
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Sir **D'Arcy Wentworth Thompson** CB FRS FRSE (2 May 1860, Edinburgh – 21 June 1948, St Andrews) was a Scottish biologist, mathematician, and classics scholar. A pioneering mathematical biologist,<sup>[1]</sup> he is mainly remembered as the author of the 1917 book, *On Growth and Form*, an influential work of striking originality and elegance. Peter Medawar, the 1960 Nobel Laureate in Medicine, called it "the finest work of literature in all the annals of science that have been recorded in the English tongue".<sup>[2]</sup>

-CB-FRS-FRSE

### Life

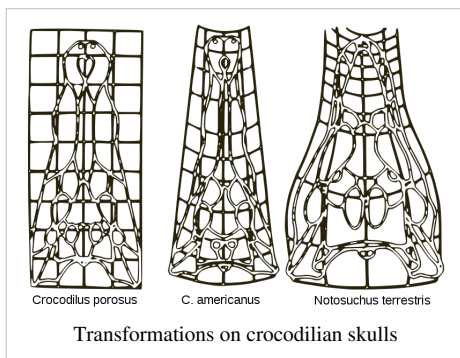
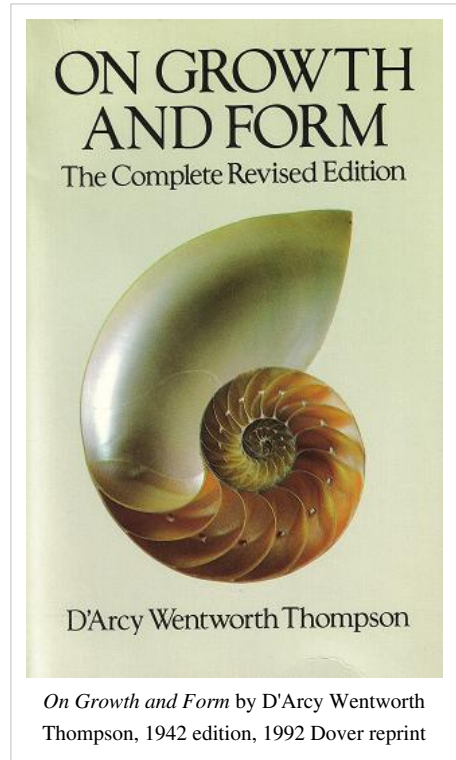
In 1878, he matriculated at University of Edinburgh to study medicine. Two years later, he shifted his studies to Trinity College in the University of Cambridge<sup>[3]</sup>, obtaining the BA in Natural Science in 1883. In 1884, he was appointed Professor of Biology at University College, Dundee, a post he held for a record 64 years. In 1917, he was appointed to the Chair of Natural History at St Andrews University. In 1896, he carried out an expedition to the Bering Straits. Elected a Fellow of the Royal Society in 1916, he was knighted in 1937 and awarded the Darwin Medal in 1946.



Sir D'Arcy  
Wentworth  
Thompson

## *On Growth and Form*

The central theme of *On Growth and Form* is that biologists of its author's day overemphasized evolution as the fundamental determinant of the form and structure of living organisms, and underemphasized the roles of physical laws and mechanics. He advocated structuralism as an alternative to survival of the fittest in governing the form of species.



On the concept of allometry, Thompson wrote:

"An organism is so complex a thing, and growth so complex a phenomenon, that for growth to be so uniform and constant in all the parts as to keep the whole shape unchanged would indeed be an unlikely and an unusual circumstance. Rates vary, proportions change, and the whole configuration alters accordingly."

Thompson pointed out example after example of correlations between biological forms and mechanical phenomena. He showed the similarity in the forms of jellyfish and the forms of drops of liquid falling into viscous fluid, and between the internal supporting structures in the

hollow bones of birds and well-known engineering truss designs. His observations of phyllotaxis (numerical relationships between spiral structures in plants) and the Fibonacci sequence has become a textbook staple.

Perhaps the most famous part of the work is chapter XVII, "The Comparison of Related Forms," where Thompson explored the degree to which differences in the forms of related animals could be described by means of relatively simple mathematical transformations.

Utterly *sui generis*, the book never quite fit into the mainstream of biological thought. It does not really include a single unifying thesis, nor, in many cases, does it attempt to establish a causal relationship between the forms emerging from physics with the comparable forms seen in biology. It is a work in the "descriptive" tradition; Thompson did not articulate his insights in the form of experimental hypotheses that can be tested.

Thompson was aware of this, saying that "This book of mine has little need of preface, for indeed it is 'all preface' from beginning to end."

This huge (the current Dover edition is 1116pp long), well-written, and extensively illustrated tome has enchanted and stimulated several generations of biologists, architects, artists, mathematicians, and, of course, those working on the boundaries of disciplines. There is a shorter (328pp) edition which preserves most of the material that is of interest to the modern reader.

## See also

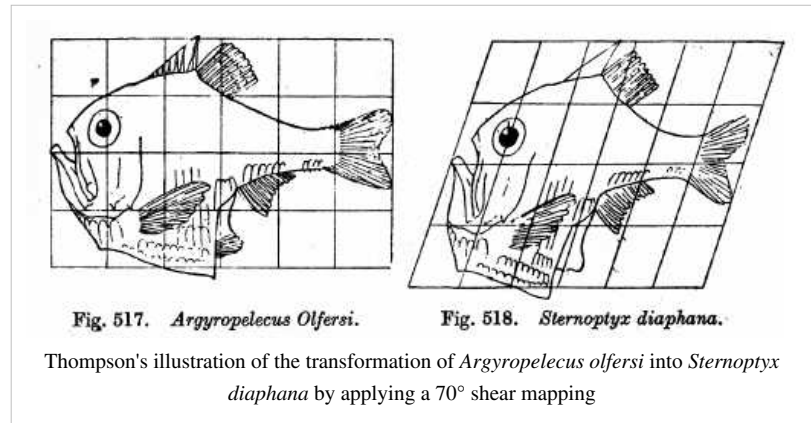
- Biophysics
- Biostatistics
- Evolutionary developmental biology
- Morphogenesis

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345 pages

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## External links

### Other works by Thompson

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# George Karreman

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| George Karreman                                                                                                                                                       |                                                           |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|
|  <p>George Karreman, the first President of the Society for Mathematical Biology</p> |                                                           |
| <b>Born</b>                                                                                                                                                           | November 4, 1921<br>Rotterdam, Netherlands                |
| <b>Died</b>                                                                                                                                                           | January 23, 1997 (aged 75)<br>Philadelphia, United States |
| <b>Residence</b>                                                                                                                                                      | Netherlands, United States                                |
| <b>Nationality</b>                                                                                                                                                    | US and Netherlands                                        |
| <b>Fields</b>                                                                                                                                                         | Physics, mathematical biology, Quantum biology            |
| <b>Institutions</b>                                                                                                                                                   | University of Pennsylvania                                |
| <b>Alma mater</b>                                                                                                                                                     | Leiden University, University of Chicago                  |
| <b>Doctoral advisor</b>                                                                                                                                               | Nicolas Rashevsky                                         |
| <b>Other academic advisors</b>                                                                                                                                        | Hendrik Anthony Kramers                                   |
| <b>Known for</b>                                                                                                                                                      | Quantum biology                                           |

**George Karreman** (b. 4 November 1921 in Rotterdam, Netherlands – 23 January 1997 in Philadelphia, USA) was a Dutch-born US physicist, mathematical biophysicist and mathematical/theoretical biologist. He was the first President of the Society for Mathematical Biology (SMB).<sup>[1]</sup>

## Biography

Karreman's father was Chief Engineer for the Dutch Merchant Marine. George Karreman studied physics and mathematics at Leiden University. In August 1948 Karreman emigrated to Chicago, USA, where he contacted Nicolas Rashevsky at the University of Chicago. He became one of Rashevsky's best PhD students in Mathematical Biophysics.<sup>[2]</sup> In 1950 Karreman underwent heart surgery at the University of Chicago and from then on had to carry an implanted pacemaker. He married Anneke Halbertsma in 1953, and they moved to Cape Cod, Massachusetts, where their daughter, Grace, was born in 1954. In slower succession, his first son, Frank Karreman was born in 1958, and then in 1962 his second son, Hubert-Jan. Later, his three children received advanced degrees from the University of Pennsylvania in several fields.

Karreman was an exceptionally devoted educator, who was always supportive of his research associates, family, and friends; he was a generous man, obviously having not forgotten Rashevsky's help in his early life at the University of Chicago.<sup>[3]</sup> He had a wide range of interests in his readings, a keen interest in the fine arts—such as paintings, was an advanced chess player, and a most devoted husband and father.<sup>[4]</sup> Between 1987 and 1997, he frequently travelled to the Pacific Northwest where his son and daughter had their homes and children.

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## Academic career

Karreman earned his B.S. in Physics and Mathematics in 1939. He completed in 1941 his M.S. in Theoretical Physics under the supervision of Hendrik Anthony Kramers at Leiden University. For the remainder of World War II he survived by tutoring students in physics and mathematics. He was awarded a University of Chicago Fellowship that supported him to complete a Ph.D. in Mathematical Biology in 1951 under the supervision of the founder of Mathematical Biophysics and Mathematical Biology, Nicolas Rashevsky.<sup>[5]</sup> Karreman was then selected as a consultant to Albert Szent-Györgyi at the Institute for Muscle Research, Marine Biological Laboratory, Woods Hole.<sup>[6]</sup> To follow his interest in mathematics applied to biology, physiology, and medicine he went to the University of Pennsylvania in Philadelphia in 1957, to take up the position of Senior Medical Research Scientist at the Eastern Research Center.<sup>[7]</sup> He was appointed associate professor of physiology at the School of Medicine in the University of Pennsylvania, where he also worked at the Bockus Research Institute at the Graduate Hospital. He was promoted to Full Professor of Physiology at the same university in 1970, where he held this position until 1983, when he became the first Professor Emeritus of Mathematical Biology.<sup>[8]</sup> His main research interests were many, but all were in related fields that included: mathematical biology and mathematical biophysics, membrane biophysics, photosynthetic mechanisms, quantum biochemistry and quantum biophysics,<sup>[9]</sup> biological energy transfer, quantum biology,<sup>[10]</sup> physiological irritability, mathematical and systems analysis of cardiovascular and other biosystems, cooperativity, threshold phenomena in biomembranes, adsorption mechanisms at membrane surfaces and ion binding to biomembranes.

After Rashevsky's passing away in 1972, Karreman was a co-founder of the Society for Mathematical Biology (SMB) in 1974—together with H. Landahl and A. Bartholomay, and in 1975 he became its first president. Karreman was also a member of several prestigious scientific societies, including the American Physiological Society, the New York Academy of Sciences, the Franklin Institute, the Society for Supramolecular Biology, Sigma Xi, the Physiological Society of Philadelphia, and the Society for Vascular System Dynamics.

## Honours

- 1974 – First President of the The Society for Mathematical Biology.<sup>[1]</sup>

## See also

- Society for Mathematical Biology
- Mathematical and theoretical biology
- Quantum biology
- Nicolas Rashevsky
- Herbert Daniel Landahl
- Hendrik Anthony Kramers

## Selected publications

- George Karreman, R.H. Steele, and Albert Szent-Gyorgyi. "On resonance transfer of excitation energy between aromatic aminoacids in proteins.", *Proc. Natl. Acad. Sci.* (1958) **44**: 140-143.
- George Karreman. "Contributions to quantum biology. I. Mobile electronic characteristics of riboflavin radicals.", *Bulletin of Mathematical Biology*, Volume **23**, Number 1/March, (1961) 55-68. Abstract <sup>[11]</sup>.
- George Karreman. "Studies in quantum biology. II. The mobile electron characteristics of tryptophan+ in relation to those of FMN–, FMNH and FMNH 2+ ". *Bulletin of Mathematical Biology*, Volume 23, Number 2/June, (1961) 135-140, DOI: 10.1007/BF02477467; Abstract <sup>[12]</sup>.
- George Karreman. "Cooperative specific adsorption of ions at charged sites in an electric field." *Bulletin of Mathematical Biology*, Volume **27**, Supplement 1 / January, 1965, 91-104., DOI: 10.1007/BF02477265.

- George Karreman. "Electronic Aspects of Quantum Biology." *Annals of the New York Academy of Sciences*, Volume **96**, *Issue on Mathematical Theories of Biological Phenomena*, Pages 1029 - 1055, published on line on 15 Dec 2006, DOI: 10.1111/j.1749-6632.1962.tb54118.x
- George Karreman. "Mathematical Biology of Physiological Excitation", *Synthese* **9**, no. 3-5 (1953): 248.
- George Karreman. "Towards a physical understanding of physiological excitation as a cooperative specific adsorption phenomenon.", *Bulletin of Mathematical Biology*, Volume **35**, Numbers 1-2 / February, 1973, 149-171, DOI: 10.1007/BF02558803.
- George Karreman, "Recent mathematical-biological studies of communication.", *Synthese* **9**, no. 3-5 (1953): 255.

## External links

- The Society for Mathematical Biology <sup>[13]</sup>
- Biographies of physicists on PlanetPhysics.org <sup>[14]</sup>

## References

- [1] <http://www.smb.org/>
- [2] <http://www.smb.org/governance/karreman.jpg> "In Memory of Our First President", the Society for Mathematical Biology
- [3] <http://www.smb.org/The Society for Mathematical Biology's Newsletter and Governance section>
- [4] Dr. George Karreman, Mathematical Biologist (<http://www.upenn.edu/almanac/v43pdf/031197.pdf>)
- [5] <http://planetphysics.org/encyclopedia/NicolasRashevsky.html> Nicolas Rashevsky's Biography
- [6] <http://www.smb.org/governance/karreman.shtml> "In Memory of GEORGE KARREMAN.", Communicated by the Chairman of Dr. Karreman's department, Professor Paul De Weer
- [7] Dr. George Karreman, Mathematical Biologist (<http://www.upenn.edu/almanac/v43pdf/031197.pdf>)
- [8] <http://www.answers.com/topic/mathematical-biology> Mathematical Biology- An outline
- [9] Karreman, George. "Studies in quantum biology. II. The mobile electron characteristics of tryptophan+ in relation to those of FMN-, FMNH and FMNH 2+." *Bulletin of Mathematical Biology*, Volume 23, Number 2/June, (1961) 135-140, DOI: 10.1007/BF02477467
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- [11] <http://www.springerlink.com/content/847x186ju2307t7m/>
- [12] <http://www.springerlink.com/content/066gkj167w842141/>
- [13] <http://www.smb.org>
- [14] <http://planetphysics.org/encyclopedia/>

# Robert Rosen

| Robert Rosen                                                                                                                                                            |                                                                                                     |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|
|  <p>Active web link to Professor Robert Rosen's large, colour photo <sup>[1]</sup></p> |                                                                                                     |
| <b>Born</b>                                                                                                                                                             | 27 June 1934<br>New York, USA                                                                       |
| <b>Died</b>                                                                                                                                                             | 28 December 1998<br>Rochester, New York, United States                                              |
| <b>Residence</b>                                                                                                                                                        | US                                                                                                  |
| <b>Citizenship</b>                                                                                                                                                      | American                                                                                            |
| <b>Nationality</b>                                                                                                                                                      | US                                                                                                  |
| <b>Ethnicity</b>                                                                                                                                                        | American                                                                                            |
| <b>Fields</b>                                                                                                                                                           | Mathematical biology, Quantum Genetics, Biophysics                                                  |
| <b>Institutions</b>                                                                                                                                                     | State University of New York (SUNY) at Buffalo, and Professor of Biophysics at Dalhousie University |
| <b>Alma mater</b>                                                                                                                                                       | University of Chicago                                                                               |
| <b>Academic advisors</b>                                                                                                                                                | Professor Nicolas Rashevsky, the Founder of Mathematical Biology in USA                             |
| <b>Notes</b><br>Active web link to Dr. Robert Rosen's photo <sup>[1]</sup>                                                                                              |                                                                                                     |

*See also arts and entertainment celebrity producer-writer-performer: Robert M. Rosen, Robert Ozn*

**Robert Rosen** (27 June 1934, - 28 December 1998, Rochester, New York) was an American theoretical biologist and Professor of Biophysics at Dalhousie University<sup>[2]</sup>.

## Biography

Robert Rosen was born on June 27, 1934 in Brownsville (a section of Brooklyn), in New York City. He studied biology, mathematics, physics, philosophy, and history-- especially the history of science-- and became a dedicated student of mathematics, physics, and biology. Then, under Professor Nicolas Rashevsky's guidance at the University of Chicago, he became a mathematical or theoretical biologist with a PhD in Mathematical Biology in 1959. His PhD research area was in Relational Biology, and he remained at the University of Chicago until 1964<sup>[3]</sup>. In 1964 Dr. Rosen was offered a full associate professorship with tenure at the University of Buffalo, now known as the State University of New York (SUNY) at Buffalo, holding a joint appointment at the Center for Theoretical Biology. In 1970, he took a sabbatical and spent a year as a Visiting Fellow at Robert Hutchins' Center for the Study of Democratic Institutions, in Santa Barbara, California. It was a seminal year for him, leading to the conception and development of what he later called Anticipatory Systems Theory, a corollary of his larger theoretical work on relational complexity, in which it is embedded. In 1975, he left SUNY at Buffalo and accepted a position at Dalhousie University, in Halifax, Nova Scotia, as a Killam Research Professor in the Department of Physiology and Biophysics, where he remained until he took early retirement in 1994.<sup>[4]</sup> He is survived by his wife, a daughter-Judith Rosen, and two sons.

He served as president of the Society for General Systems Research, (now known as ISSS), in 1980-81. See also the link to Dr. Robert Rosen's photo <sup>[1]</sup>

## Research

Rosen's research was concerned with the most fundamental aspects of biology, specifically the question "What is life?" or "Why are living organisms alive?". Major themes in the work of Robert Rosen were:

- developing a specific definition of complexity that is based on relations and, by extension, principles of organization
- developing a rigorous theoretical foundation for living organisms as "anticipatory systems"

Rosen believed that the contemporary model of physics - which he thought to be based on an outdated Cartesian and Newtonian world of mechanisms - was inadequate to explain or describe the behavior of biological systems; that is, one could not properly answer the fundamental question "*What is life?*" from within a scientific foundation that is entirely reductionistic. He thought that approaching organisms with what he considered to be excessively reductionistic scientific methods and practices sacrifices the whole in order to study the parts, but what Rosen thought was that the whole could not be recaptured once the biological organization had been destroyed. His conclusion was that the very thing about living organisms biologists should be studying, the organization, was the first aspect of all biological systems to be thrown away in reductionist analysis. This is regarded as a limitation of the part of contemporary science which regards the machine or automaton as a model for all systems in the universe. Rosen came to regard the machine metaphor as the single biggest impediment to scientific exploration of questions in biology and concluded that the paradigm needs to be expanded beyond purely reductionist capabilities. In order to do this properly, he said there must be a sound theoretical foundation underlying the expansion and that relational complexity provided such a foundation. So it was that, rather than biology being a mere subset of the already known physics, it turned out that biology might have profound lessons for physics, and also science, in general.<sup>[5]</sup>

## Relational biology

Rosen's work proposes a methodology that he called "*Relational Biology*" which needs to be developed in addition to the current reductionistic approaches to science by molecular biologists. ("Relational" is a term he correctly attributes to Nicolas Rashevsky who published several papers on the importance of set-theoretical relations<sup>[6]</sup> in biology prior to Rosen's first reports on this subject). Rosen's relational approach to Biology is an extension and amplification of Nicolas Rashevsky's treatment of n-ary relations in, and among, organismic sets that he developed over two decades as a representation of both biological and social 'organisms'. Rosen's relational biology maintains that organisms, and indeed all systems, have a distinct quality called "*organization*" which is not part of the language of reductionism, as for example in molecular biology, although it is increasingly employed in systems biology. It has to do with more than purely structural or material aspects. For example, organization includes all relations between material parts, relations between the effects of interactions of the material parts, and relations with time and environment, to name a few. Many people sum up this aspect of complex systems<sup>[7]</sup> by saying that "*the whole is more than the sum of the parts*". Relations between parts and between the effects of interactions must be considered as additional 'relational' parts, in some sense. Rosen said that organization must be independent from the material particles which seemingly constitute a living system. As he put it: "The human body completely changes the matter it is made of roughly every 8 weeks, through metabolism and repair. Yet, you're still you-- with all your memories, your personality... If science insists on chasing particles, they will follow them right through an organism and miss the organism entirely," (as told to his daughter, Ms. Judith Rosen<sup>[8]</sup>). Rosen's abstract relational biology approach focuses on a definition of living organisms, and all complex systems, in terms of their internal "organization" as open systems that cannot be reduced to their interacting components because of the multiple relations between metabolic and repair components that govern the organism's complex biodynamics. He deliberately chose the 'simplest' graphs and categories for his representations of Metabolic-Replication Systems in small categories of sets endowed only

with the discrete topology of sets, envisaging this choice as the most general and less restrictive. It turns out however that the categories of **(M,R)**-systems are Cartesian closed, and may be considered in a very strict mathematical sense as subcategories of the category of sequential machines or automata, in a somewhat ironical vindication of the French philosopher Descartes' supposition that **all animals are only elaborate machines** or *mechanisms*. The latter, mechanistic view prevails even today in most of general biology, but no longer in sociology and psychology where reductionist approaches have failed and fallen out of favour since the early 1970's.

### Rosen's concept of complexity and complex scientific models

The clarification of the distinction between simple and complex scientific models became in later years a major goal of Rosen's published reports; Rosen maintained that modeling is at the very essence of science and thought. His book *Anticipatory Systems* describes, in detail, what he termed the *modeling relation*. He showed the deep differences between a true modeling relation and a simulation (that is not based on such a modeling relation). In mathematical biology he is known as the originator of a class of relational models of living organisms, called "**(M,R)**-systems" that he devised, which he claimed that capture the minimal, or basic, capabilities that a material system would need in order to specify the simplest functional organisms, that are commonly said to be "alive". In this kind of system, **M** stands for the metabolic, and **R** stands for the 'repair', components or subsystems of a simple organism, (such as for example active 'repair' RNA molecules). Thus, his mode for determining life, or 'defining' life, in any given system is a functional one, not a material one, although he did consider in his 1970s published reports specific *dynamic realizations* of the simplest "**(M,R)**-systems" in terms of enzymes (**M**), RNA (**R**), and functional, duplicating DNA (his "**β**-mapping"). He went, however, even farther in this direction by claiming that when studying a complex system, one "can throw away the matter and study the organization order" to learn those things that are essential to defining in general an entire class of systems. This has been, however, taken too literally by a few of his former students who have not completely assimilated Robert Rosen's injunction of the need for a theory of *dynamic realizations* of such abstract components in specific molecular form in order to close the modeling loop for the simplest functional organisms (such as, for example, single-cell algae or microorganisms)<sup>[9]</sup>. He supported this claim (that he actually attributed to Nicolas Rashevsky) based on the fact that living organisms are a class of systems with an extremely wide range of material "ingredients", different structures, different habitats, different modes of living and reproduction, and yet we are somehow able to recognize them all as 'living', or functional organisms, without being however 'vitalists'. His approach, just like Rashevsky's latest theories of organismic sets<sup>[10], [11]</sup>, emphasizes biological organization over molecular structure in an attempt to bypass the *structure-functionality relationships* that are important to all experimental biologists, including physiologists. In contrast, a study of the specific material details of any given organism, or even of a whole species, will only tell us about how that type of organism "does it". Such a study doesn't approach what is common to all physiologically-functional organisms, i.e. "life". Relational approaches to theoretical biology would therefore allow us to study organisms in ways that preserve those essential qualities that we are trying to learn about, and that are common only to *functional* organisms. One needs conclude that Robert Rosen's approach belongs conceptually to what is now known as Functional Biology, as well as Complex Systems Biology, *albeit* in a highly abstract, mathematical form.

### Quantum Biochemistry and Quantum Genetics

Rosen also questioned what he believed to be many aspects of mainstream interpretations of biochemistry and genetics. He objects to the idea that functional aspects in biological systems can be investigated via a material focus. One example: Rosen disputes that the functional capability of a biologically active protein can be investigated purely using the genetically encoded sequence of amino acids. This is because, he said, a protein must undergo a process of "folding" to attain its characteristic three-dimensional shape before it can become functionally active in the system. Yet, only the amino acid sequence is genetically coded. The mechanisms by which proteins fold are not completely known. He concluded, based on examples such as this, that phenotype cannot always be directly attributed to genotype and that the chemically active aspect of a biologically active protein relies on more than the sequence of

amino acids, from which it was constructed: there must be some other important factors at work, that he did not however attempt to specify or pin down.

Certain questions about Rosen's mathematical arguments were raised in a paper authored by Christopher Landauer and Kirstie L. Bellman which claimed that some of the mathematical formulations used by Rosen are problematic from a logical viewpoint. One notes however that such issues were also raised long time ago by Bertrand Russel and Alfred North Whitehead in their famous "*Principia Mathematica*" in relation to antinomies of set theory. As Rosen's mathematical formulation in his earlier papers was also based on set theory and the category of sets such issues have naturally re-surfaced. However, these issues have now been addressed by Robert Rosen in his recent book "*Life, Itself*", published posthumously in 2000. Furthermore, such basic problems of mathematical formulations of **(M,R)**--systems had already been resolved by other authors as early as 1973 by utilizing the Yoneda lemma in category theory, and the associated functorial construction in categories with (mathematical) structure<sup>[12] [13]</sup>. Such general category theory extensions of **(M,R)**-systems that avoid set theory paradoxes are based on William Lawvere's categorical approach and its extensions to higher-dimensional algebra. The mathematical and logical extension of *metabolic-replication systems* to generalized **(M,R)**-systems, or **G-MRs**, also involved a series of acknowledged letters exchanged between Robert Rosen and the latter authors during 1967--1980s, as well as letters exchanged with Nicolas Rashevsky up to 1972.

"*Life, Itself*" and also his subsequent book "*Essays on Life Itself*", discuss also rather critically certain quantum genetics issues such as those introduced by Erwin Schrödinger in his famous early 1945 book "What Is Life?". (Note, by Judith Rosen, who owns the copyrights to her father's books: Some of the confusion is due to known errata introduced into the book, "Life, Itself," by the publisher. For example, the diagram that refers to "(M,R)-Systems" has more than one error; errors which do not exist in Rosen's manuscript for the book. These errata were made known to Columbia University Press when the company switched from hardcover to paperback version of the book (in 2006) but the errors were not corrected and remain in the paperback version as well. The book "Anticipatory Systems; Philosophical, Mathematical, and Methodological Foundations" has the same diagram, correctly represented.)

## See also

- A Bibliography of Robert Rosen's publications.<sup>[14]</sup>
- system theory
  - Cybernetics and Systems Thinkers<sup>[15]</sup> overview by the Principia Cybernetica Web.
  - Society for General Systems Research
- Mathematical biology and Mathematical biophysics
  - Nicolas Rashevsky
  - Category theory
  - Category of sets
  - Society for Mathematical Biology
- complexity theory
  - Complex Systems Biology
- Quantum biology
  - Quantum Genetics
  - Quantum Biochemistry
- philosophy of science
  - What Is Life?
  - Ontology
  - Autopoiesis



## Publications

Rosen has written several books and articles. A selection of his published books is as follows:

- 1970, *Dynamical Systems Theory in Biology* New York: Wiley Interscience.
- 1970, *Optimality Principles*, Rosen Enterprises
- 1978, *Fundamentals of Measurement and Representation of Natural Systems*, Elsevier Science Ltd,
- 1985, *Anticipatory Systems: Philosophical, Mathematical and Methodological Foundations*. Pergamon Press.
- 1991, *Life Itself: A Comprehensive Inquiry into the Nature, Origin, and Fabrication of Life*, Columbia University Press

Published posthumously:

- 2000, *Essays on Life Itself*, Columbia University Press.
- 2003, "Anticipatory Systems; Philosophical, Mathematical, and Methodical Foundations", Rosen Enterprises
- 2003, *Rosennean Complexity*, Rosen Enterprises.
- 2003, *The Limits of the Limits Of Science*, Rosen Enterprises

## Notes

- [1] <http://www.people.vcu.edu/~mikuleck/bobrosen.gif>
- [2] Autobiographical Reminiscences of Robert Rosen, *Axiomathes* (2006). Volume 16, Numbers 1-2/ March, 2006, DOI:10.1007/s10516-006-0001-6, pages 1-23 (<http://www.springerlink.com/content/fk37800274466085/>); Robert Rosen about his own educational background, his philosophy of science, and his general point of view.]
- [3] "Autobiographical Reminiscences of Robert Rosen" (<http://www.rosen-enterprises.com/RobertRosen/rrosenautobio.html>)
- [4] In Memory of Dr. Robert Rosen (<http://communications.medicine.dal.ca/connection/feb1999/rosen.htm>), Feb 1999, retrieved Oct 2007.
- [5] [<http://www.panmere.com/rosen/rosensum.htm> Robert Rosen -- Biology, Complexity and Physics
- [6] Jon Awbrey "Relation theory" (the logical approach to relation theory) (<http://planetphysics.org/encyclopedia/RelationTheory.html>)
- [7] [http://www.springerlink.com/content/n8gw445012267381/I.C. Baianu, \(Editor\) "Robert Rosen's Work and Complex Systems Biology." Axiomathes \(2006\) Volume 16, Numbers 1-2 / March, 2006, DOI: 10.1007/s10516-005-4204-z , pages 25-34](http://www.springerlink.com/content/n8gw445012267381/I.C. Baianu, (Editor) \)
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- What Is Life?

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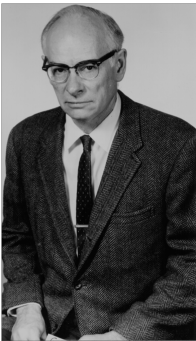
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## External links

- "Autobiographical Reminiscences of Robert Rosen", *Axiomathes* (2006). Volume **16**, Numbers 1-2/ March, 2006, DOI:10.1007/s10516-006-0001-6, pages 1-23 (<http://www.springerlink.com/content/fk37800274466085/>); *Robert Rosen about his own educational background, his philosophy of science, and his general point of view.*]
- Autobiographical Reminiscences of Robert Rosen (<http://www.rosen-enterprises.com/RobertRosen/rrosenautobio.html>)
- "Reminiscences of Nicolas Rashevsky". (Late) 1972. by Robert Rosen.
- Robert Rosen's Biography (<http://planetphysics.org/encyclopedia/RobertRosen.html>)
- Jon Awbrey "Relation theory" (the logical approach to relation theory) (<http://planetphysics.org/encyclopedia/RelationTheory.html>)
- The Society for Mathematical Biology (<http://www.smb.org/>)
- "The Bulletin of Mathematical Biophysics" (<http://www.springerlink.com/content/x513p402w52w1128/>)
- Rosen: Complexity and Life (<http://www.panmere.com/>"Robert) A website exploring the work of Rosen.
- "Robert Rosen's Work and Complex Systems Biology." *Axiomathes* (2006) Volume 16, Numbers 1-2 / March, 2006 DOI: 10.1007/s10516-005-4204-z , pages 25-34. (<http://www.springerlink.com/content/n8gw445012267381/>)- A tribute to Robert Rosen by I.C. Baianu, (Editor of *Axiomathes*- Special Robert Rosen and Complexity Issue in 2006), Springer: Berlin and New York.
- Robert Rosen: June 27, 1934 — December 30, 1998 (<http://www.people.vcu.edu/~mikuleck/Rosenreq.html>) by Aloisius Louie.
- *Robert Rosen: The well posed question and its answer: why are organisms different from machines?* (<http://www.people.vcu.edu/~mikuleck/PPRISS3.html>) An essay by Donald C. Mikulecky.
- Panmere website on Rosennean Complexity ([http://www.panmere.com/?page\\_id=10](http://www.panmere.com/?page_id=10)): "Judith Rosen's website provides free biographical information, discussions of her father's work, and also free reprints of Robert Rosen's work".
- Paper ([http://content.aip.org/APCPCS/v627/i1/59\\_1.html](http://content.aip.org/APCPCS/v627/i1/59_1.html)) by Christopher Landauer and Kirstie L. Bellman criticising some of Rosen's mathematical formulations, followed by attempts to improve the formulations.

# Herbert Daniel Landahl

| Herbert Daniel Landahl                                                                                                            |                                                                         |
|-----------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|
|  <p>Professor Herbert Daniel Landahl at UCSF</p> |                                                                         |
| <b>Born</b>                                                                                                                       | 23 April 1913<br>Fancheng, China                                        |
| <b>Residence</b>                                                                                                                  | US                                                                      |
| <b>Citizenship</b>                                                                                                                | USA                                                                     |
| <b>Nationality</b>                                                                                                                | USA                                                                     |
| <b>Ethnicity</b>                                                                                                                  | American born in China                                                  |
| <b>Fields</b>                                                                                                                     | Mathematical biology, Biophysicist, Physics                             |
| <b>Institutions</b>                                                                                                               | University of Chicago, University of California at San Francisco        |
| <b>Alma mater</b>                                                                                                                 | University of Chicago                                                   |
| <b>Doctoral advisor</b>                                                                                                           | Nicolas Rashevsky                                                       |
| <b>Known for</b>                                                                                                                  | Mathematical biophysics of neurons and the central nervous system (CNS) |
| <b>Notable awards</b>                                                                                                             | Former President of The Society for Mathematical Biology, USA           |

**Herbert Daniel Landahl, Ph.D.** is an American mathematical biophysicist who was born in Fancheng, China, on April 23, 1913. He obtained with *Magna Cum Laude* his AB degree at St. Olaf College in 1934, and then earned this SM in Physics at the University of Chicago in 1936. He then became very interested in mathematical biophysics and was the world's first PhD student to graduate in Mathematical Biophysics at the University of Chicago in 1941 under the supervision of Professor Nicolas Rashevsky, the Founder of Mathematical Biophysics and Mathematical Biology.

## Academic career

Herbert D. Landahl was hired at first in 1937 as a Research Assistant in the Psychometrics Laboratory at the University of Chicago, and then transferred to change his research to the field of mathematical biophysics as a Research Assistant in the Department of Physiology between 1939 and 1942. After graduation in 1941 with a PhD in Mathematical Biophysics, he was able to continue as a Research Associate of Professor Nicolas Rashevsky between 1942 and 1945. He was then promoted in rapid succession to a tenured track Assistant Professorship in 1945, and to a tenured position of Associate Professor and full Professor of Mathematical Biology between 1948 and 1958. In 1945 he co-authored with Scott Alston Householder a fundamental book on the "*Mathematical biophysics of the central nervous system.*" (The Principia Press, 1945)<sup>[1]</sup>. He became a full Professor of Biophysics in 1964 and continued to work as full professor at the University of Chicago (UC) until 1968 when he was lured by the University of California at San Francisco (UCSF) after the former UC president declined to promote him to the

Chair of the Committee for Mathematical Biology as Nicolas Rashevsky's successor upon the latter's planned retirement in 1969. As a result of the ensuing disagreement between Rashevsky and the UC president, Nicolas Rashevsky resigned from his UC position in 1968 and moved to Ann Arbor in Michigan. Dr. Landahl took up his new position of full Professor of Biophysics and Biomathematics in 1969 at UCSF where he became a Professor Emeritus in 1980, and continues today his research and related supervisory/ advisory activities.

### **Main research interests**

Dr. Landahl's research interests were, and are, focused on the dynamics of neural networks and the central nervous system (CNS). He also studied the biophysics of cell division, biological effects of radiation, population interactions in ecology, biological clocks and insulin biosynthesis. He published extensively in these fields as detailed in the UCSF official Register of the Herbert Daniel Landahl Papers, 1947-88Landahl (Herbert D.)<sup>[2][3]</sup>

### **Honors and society memberships**

Dr. Landahl cofounded in 1972 with George Karreman and Anthony Bartholomay "The Society for Mathematical Biology" (SMB), and served as SMB's first Vice-President between 1972 and 1982. He also served between 1973 and 1981 as the Chief Editor of the Bulletin of Mathematical Biology-the main publishing journal of SMB.

Dr. Landahl is also member of the Biometric Society, the Biophysical Society, and the New York Academy of Sciences. He was elected a Fellow of the American Association for the Advancement of Science, (AAAS).

### **See also**

- Mathematical biology
  - Nicolas Rashevsky
  - George Karreman
  - University of Chicago
  - University of California at San Francisco
  - Theoretical biology
  - The Society for Mathematical Biology
  - Bulletin of Mathematical Biology<sup>[6]</sup>
  - Neurophysiology
  - Neurons
  - Neurodynamics
  - Population dynamics
  - Psychometrics
  - Psychophysics
  - Biophysics
  - SIAM
  - Biophysical Society
-

## Further reading

- Alston Scott Householder and Herbert Daniel Landahl. 1945. *Mathematical biophysics of the central nervous system*, The Principia Press. <sup>[4]</sup>
- Landahl, H.D. 1987. Approximate Solution for Capillary Exchange Models with and without Axial Mixing., *Bull. Math. Biology*, **49**, (6):719-728.
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- Landahl, Herbert Daniel. "*Studies in the mathematical biophysics of cell division*". (1941), Thesis (Ph. D.)--University of Chicago, Department of Physiology.
- Karreman, George, and Landahl, H. D. On the mathematical biology of excitation phenomena. *Cold Springs Harbor Symposia on Quantitative Biology. XVII: The Neuron* (1952), p. 293.

## External links

- The International Society for Mathematical Biology Home Page <sup>[13]</sup>
- American Association for the Advancement of Science, AAAS
- University of California, San Francisco, UCSF
- University of Chicago
- American Association for the Advancement of Science website <sup>[5]</sup>
- 1973 Constitution of the AAAS <sup>[6]</sup>

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- [3] <http://texts.cdlib.org:8088/xtf/data/13030/mg/tf5x0nb4mg/tf5x0nb4mg.xml>.landahlh.xml of Register of the Herbert Daniel Landahl Papers, 1947-88Landahl (Herbert D.)
- [4] <http://www.archive.org/details/mathematicalbiop00hous>
- [5] <http://www.aaas.org>
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# Anatol Rapoport

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**Anatol Rapoport** (Russian: Анато́лий Бори́сович Рапопо́рт, born May 22, 1911- January 20, 2007) was a Russian-born American Jewish mathematical psychologist. He contributed to general systems theory, mathematical biology and to the mathematical modeling of social interaction and stochastic models of contagion.

## Biography

Rapoport was born in Lozovaya, Russia. In 1922, he came to the United States, and in 1928 he became a naturalized citizen. He started studying music in Chicago and continued with piano, conducting and composition at the Vienna Hochschule für Musik where he studied from 1929 to 1934. However, due to the rise of Nazism, he found it impossible to make a career as a pianist.<sup>[1]</sup>

He shifted his career into mathematics, getting a Ph.D. degree in mathematics under Nicolas Rashevsky at the University of Chicago in 1941. According to the *Toronto Globe and Mail*, he was a member of the American Communist Party for three years, but quit before enlisting in the U.S. Army Air Corps in 1941, serving in Alaska and India during World War II.<sup>[2]</sup>

After the war, he joined the Committee on Mathematical Biology at the University of Chicago (1947–1954), publishing his first book, *Science and the Goals of Man*, co-authored with semanticist S. I. Hayakawa in 1950. He also received a one-year fellowship at the prestigious Center for Advanced Study in the Behavioral Sciences (Stanford, California).

From 1955 to 1970 Rapoport was Professor of Mathematical Biology and Senior Research Mathematician at the University of Michigan, as well as founding member, in 1955, of the Mental Health Research Institute (MHRI) at the University of Michigan. In 1970 Rapoport moved to Toronto to avoid the war-making ways of the Vietnam-era United States. He was appointed professor of mathematics and psychology at the University of Toronto, 1970-1979. He lived in bucolic Wychwood Park overlooking downtown Toronto, a neighbour of Marshall McLuhan. On his retirement from the University of Toronto, he became director of the Institute of Advanced Studies (Vienna) until 1983.

In 1954, Anatol Rapoport cofounded the Society for General Systems Research, along with the researchers Ludwig von Bertalanffy, Ralph Gerard, and Kenneth Boulding. He became president of the Society for General Systems Research in 1965.

Anatol Rapoport died of pneumonia in Toronto. He is survived by his wife Gwen, daughter Anya, and sons Alexander and Anthony.

## Work

Rapoport contributed to general systems theory, mathematical biology and to the mathematical modeling of social interaction and stochastic models of contagion. He combined his mathematical expertise with psychological insights into the study of game theory, social networks and semantics.

Rapoport extended these understandings into studies of psychological conflict, dealing with nuclear disarmament and international politics. His autobiography, *Certainties and Doubts: A Philosophy of Life*, was published in 2001.

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## Game theory

Rapoport had a versatile mind, working in mathematics, psychology, biology, game theory, social network analysis, and peace and conflict studies. For example, he pioneered in the modeling of parasitism and symbiosis, researching cybernetic theory. This went on to give a conceptual basis for his lifelong work in conflict and cooperation.

Among many other well-known books on fights, games, violence and peace, Rapoport was the author of over 300 articles and of *Two-Person Game Theory* (1966) and *N-Person Game Theory* (2001). He analyzed contests in which there are more than two sets of conflicting interests, such as war, diplomacy, poker or bargaining. His work led him to peace research (see below), including books on *The Origins of Violence* (1989) and *Peace, An Idea Whose Time Has Come* (1993), both written at the University of Toronto.

He won a computer tournament in the 1980s, based on Robert Axelrod's *The Evolution of Cooperation*. This sought to understand how cooperation could emerge through evolution. Rapoport's entry, *Tit-For-Tat* has only four lines of code. The program opens by cooperating with its opponent. It then plays exactly as the other side played in the previous game. If the other side defected in the previous game, the program also defects; but only for one game. If the other side cooperates, the program continues to cooperate. According to *Peace Magazine* author/editor Metta Spencer, the program "punished the other player for selfish behaviour and rewarded her for cooperative behaviour—but the punishment lasted only as long as the selfish behaviour lasted. This proved to be an exceptionally effective sanction, quickly showing the other side the advantages of cooperating. It also set moral philosophers to proposing this as a workable principle to use in real life interactions."

His children report that he was a strong chess player but a bad poker player because he non-verbally revealed the strength of his hands.<sup>[2]</sup>

## Social network analysis

Anatol Rapoport was an early developer of social network analysis. His original work showed that one can measure large networks by profiling traces of flows through them. This enables learning about the speed of the distribution of resources, including information, and what speeds or impedes these flows—such as race, gender, socioeconomic status, proximity and kinship.<sup>[3]</sup> This work linked social networks to the diffusion of innovation, and by extension, to epidemiology. Rapoport's empirical work traced the spread of information within a school. It prefigured the study of Six degrees of separation, by showing the rapid spread of information in a population to almost all—but not all—school members (see references below).

## Conflict and peace studies

According to Thomas Homer-Dixon in the *Toronto Globe and Mail*, Rapoport "became anti-militarist quite soon after the war. [WWII]. The idea of military values became anathema." He was a leading organizer of the first teach-ins against the Vietnam War at the University of Michigan, a model that spread rapidly throughout North America. He told at a teach-in: "By undertaking the war against Vietnam, the United States has undertaken a war against humanity.... This war we shall not win." (*Ann Arbor News*, April 1967). He said he was an abolitionist, rather than a total pacifist: "I'm for killing the institution of war".

Rapoport returned to the University of Toronto to become the founding (and unpaid) Professor of Peace and Conflict Studies programme, working with George Ignatieff and Canada's Science for Peace organization. As its sole professor at the start, he used a rigorous, interdisciplinary approach to the study of peace, integrating mathematics, politics, psychology, philosophy, science and sociology. His main concern was to legitimize peace studies as a worthy academic pursuit. The Trudeau Centre for Peace and Conflict Studies continued to flourish at the University of Toronto under the leadership of Thomas Homer-Dixon, and, from 2008, under Ron Levi. When Rapoport began, there were one (unpaid) professor and twelve students. Now, there are three (paid) professors and ninety students.<sup>[4]</sup>

Rapoport's students report that he was an engaged and inspiring professor who captured their attention, imagination and interest with his wide-ranging knowledge, passion for the subject, good humor, kind and generous spirit, attentiveness to student concerns and animated teaching style.<sup>[5]</sup>

In 1981, Rapoport co-founded the international NGO *Science for Peace*, and in 1984 he created the famous tit for tat strategy for the iterated prisoner's dilemma tournament held by Robert Axelrod that year. He was recognized in the 1980s for his contribution to world peace through nuclear conflict restraint via his game theoretic models of psychological conflict resolution. He won the Lenz International Peace Research Prize in 1976.

## Publications

Rapoport's books and articles include:

Books:

- 1975, *Semantics*, Crowell, 1975.<sup>[6]</sup>
- 2000, *Certainties and Doubts : A Philosophy of Life*, Black Rose Books, Montreal, 2000: His autobiography.

Articles, a selection:

- 1953, "Spread of information through a population with sociostructural bias: I. Assumption of transitivity." in: *Bulletin of Mathematical Biophysics*, 15, 523-533.
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- 1989, with Y. Yuan, "Some Aspects of Epidemics and Social Nets." Pp. 327–348 in *The Small World*, ed. by Manfred Kochen. Norwood, NJ: Ablex.

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- Chesmak Farhoumand-Sims, "Memories of Anatol Rapoport." *Peace Magazine*, April 2007, p. 14
- Alisa Ferguson, "Rapoport was Renowned Mathematical Psychologist, Peace Activist." *University of Toronto Bulletin*, February 20, 2007.

## External links

- Science for Peace website <sup>[7]</sup>
- History of Science for Peace <sup>[8]</sup>
- Profile of Anatol Rapoport <sup>[9]</sup>
- Farhoumand-Sims, Chesmak (April 2007). "Memories of Anatol Rapoport" <sup>[10]</sup>. *Peace Magazine*: p14. Retrieved 2008-05-03.



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  - [3] Harrison White, *Identity and Control*, 2nd ed., Princeton, NJ: Princeton University Press, 2007
  - [4] Alisa Ferguson, "Rapoport was Renowned Mathematical Psychologist, Peace Activist," *University of Toronto Bulletin*, February 20, 2007
  - [5] Chesmak Farhoumand-Sims, "Memories of Anatol Rapoport," *Peace Magazine*, April 2007, p. 14
  - [6] This book about general semantics along the lines of S.I. Hayakawa's *Language in Thought and Action* and more technical (mathematical and philosophical) material. A valuable survey.
  - [7] <http://www.scienceforpeace.ca/>
  - [8] <http://www.peacemagazine.org/archive/v03n5p27.htm>
  - [9] <http://www.isss.org/lumrapo.htm>
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# Walter M.Elsasser

For the wine "Elsasser," see Alsace wine

| Walter Maurice Elsasser                                                                                                                                              |                                                                                                                                                   |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| <div><p>Walter Maurice Elsasser, PhD, physicist and theoretical biologist</p></div> |                                                                                                                                                   |
| Born                                                                                                                                                                 | 20 March 1904<br>Mannheim, Germany                                                                                                                |
| Died                                                                                                                                                                 | 14 October 1991<br>Baltimore, United States                                                                                                       |
| Fields                                                                                                                                                               | physics                                                                                                                                           |
| Known for                                                                                                                                                            | geodynamo theory, quantum physics, theory of radioactive nuclei,theoretical biology, logical classes in mathematical biology and systems biology. |
| Influenced                                                                                                                                                           | theoretical biology, Nobel laureates                                                                                                              |
| <b>Notes</b> <div>Active link to Dr. Walter Maurice Elsasser's photo <sup>[1]</sup></div>                                                                            |                                                                                                                                                   |

**Walter Maurice Elsasser** (born 20 March 1904, in Mannheim, Germany; died 14 October 1991, in Baltimore) was a physicist and is considered "father" of the geodynamo theory. Long before he became known for his geodynamo theory, while in Göttingen in the 1920s, he has suggested the experiment to test the wave aspect of electrons. This suggestion of Elsasser was later communicated by his senior colleague from Göttingen (Nobel Prize recipient Max Born) to physicists in England. This explained the results of the Davisson-Germer and Thomson experiments later awarded with the Nobel Prize in Physics. In 1935, while working in Paris, Elsasser calculated the binding energies of protons and neutrons in heavy radioactive nuclei. Wigner, Jensen and Meyer received the Nobel in 1963 for work developing out of Elsasser's initial formulation. Elsasser therefore came quite close to a Nobel prize on two occasions.

Over 1946-1947, Elsasser published papers outlining the theory that the Earth's electromagnetic field is powered by eddy currents at the planet's liquid core. This had been developed from around 1941 onwards, partly in his spare time during his scientific war service with the US Signal Corps.

In his later years, Elsasser became interested in what is now called systems biology and contributed a series of articles to Journal of Theoretical Biology.<sup>[2] [3] [4] [5] [6] [7] [8]</sup> The final version of his thoughts on this subject can be found in his book Reflections on a Theory of Organisms, published in 1987 and again posthumously with a new forward by Harry Rubin in 1998.

## Biotonic laws

A **biotonic law**, a phrase coined by Elsasser, is a law of nature which cannot be contained in the laws of physics.<sup>[9]</sup>

Elsasser's biological work is still quite controversial, and in fact sits in an odd relationship to the field of systems biology he helped to found. Central to Elsasser's biological thought is the notion of the astronomical complexity of the cell. Elsasser deduced from this that any investigation of a causative chain of events in a biological system will reach a "terminal point", where the number of possible inputs into the chain will overwhelm the capacity of the scientist to make predictions, even with the most powerful computers. This might seem like a counsel of despair, but in fact Elsasser was not calling for the abandonment of biology as a worthwhile research arena, but rather for a different kind of biology where molecular causal chains are no longer the main focus of study. Correlation between supra-molecular events would become the main data source.

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- *Atom and Organism. A New Approach to Theoretical Biology*, (1966) Princeton University Press
- *The Chief Abstractions of Biology*, (1975), North Holland, Amsterdam.
- *Memoirs of a Physicist in the Atomic Age*, (1978)
- *The role of individuality in biological theory*, (1970) in *Towards a Theoretical Biology vol.3* Edinburgh University Press
- *Reflections on a Theory of Organisms. Holism in Biology*, (1998) Johns Hopkins University Press (JHU).

The Olin Hall at the Johns Hopkins University has a Walter Elsasser Memorial in the lobby.

## Biographical Entry

- Beyler R & Gatherer D (2007) *Walter Elsasser (biography)*. In: *Dictionary of Scientific Biography*, new ed. New York: Charles Scribner's Sons Inc.

## Web pages

- Extensive biography at The National Academies Press<sup>[10]</sup>
- Gatherer D: Finite universe of discourse. The systems biology of Walter Elsasser. *The Open Biology Journal* 2 4-15<sup>[11]</sup>

## External links

- Oral History interview transcript with Walter Elsasser 29 May 1962, American Institute of Physics, Niels Bohr Library and Archives<sup>[12]</sup>

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- [2] Elsasser, WM (1983). "Biological application of the statistical concepts used in the Second Law". *Journal of theoretical biology* **105** (1): 103–16. doi: 10.1016/0022-5193(83)90427-7 ([http://dx.doi.org/10.1016/0022-5193\(83\)90427-7](http://dx.doi.org/10.1016/0022-5193(83)90427-7)). PMID 6656269 (<http://www.ncbi.nlm.nih.gov/pubmed/6656269>).
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## Brian Goodwin

**Brian Carey Goodwin** (1931 – 15 July 2009) was a Canadian mathematician and biologist.

He was Professor Emeritus at the Open University.

### Biography

Brian Goodwin was born in Montreal, Canada in 1931. He studied biology at McGill University and then emigrated to the UK, under a Rhodes Scholarship for studying mathematics at Oxford. He got his PhD. at the University of Edinburgh. His first teaching job, in mathematics, was at Oxford University and then moved to Sussex University until 1983 when he became a full professor at the Open University in Milton Keynes until retirement in 1992. Thereafter, he taught at the Schumacher College in Devon, UK. Goodwin has also a research position at the MIT and was a long time visitor of several institutions including the UNAM in Mexico City. He was a founding member of the Santa Fe Institute in New Mexico where he also served as a external faculty for several years<sup>[1]</sup>

Brian Goodwin died in hospital in 2009, after surgery resulting from a fall from his bike.<sup>[2]</sup>

### Publications

#### Books

- 1989. *Theoretical Biology: Epigenetic and Evolutionary Order for Complex Systems* with Peter Saunders, Edinburgh University Press, 1989, ISBN 0852246005
- 1994. *Mechanical Engineering of the Cytoskeleton in Developmental Biology (International Review of Cytology)*, with Kwang W. Jeon and Richard J. Gordon, Academic Press, London 1994, ISBN 0123645530
- 1996. *Form and Transformation: Generative and Relational Principles in Biology*, Cambridge Univ Press, 1996.
- 1997. *How the Leopard Changed its Spots: The Evolution of Complexity*, Scribner, 1994, ISBN 0025447106 (German: *Der Leopard, der seine Flecken verliert*, Piper, München 1997, ISBN 3492038735)
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- 2007. *Nature's Due: Healing Our Fragmented Culture*, Floris Books, 2007, ISBN 0863155960



Brian Goodwin (on the right).

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## External links

- A New Science of Qualities: a Talk With Brian Goodwin <sup>[3]</sup>
- An interview with Professor Brian Goodwin <sup>[4]</sup>

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- [2] Professor Brian Goodwin (<http://www.schumachercollege.org.uk/news/professor-brian-goodwin>), Schumacher College
- [3] [http://www.edge.org/3rd\\_culture/goodwin/goodwin\\_p1.html](http://www.edge.org/3rd_culture/goodwin/goodwin_p1.html)
- [4] <http://ngin.tripod.com/article8.htm>

# Warren Sturgis McCulloch

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**Warren Sturgis McCulloch** (November 16, 1898 – September 24, 1969) was an American neurophysiologist and cybernetician, known for his work on the foundation for certain brain theories and his contribution to the cybernetics movement.<sup>[1]</sup>

## Biography

Warren Sturgis McCulloch was born in Orange, New Jersey, in 1898. He attended Haverford and studied philosophy and psychology at Yale, where he received an A.B. degree in 1921. He continued to study psychology at Columbia and received a M.A. degree in 1923. Receiving his MD in 1927 from the College of Physicians and Surgeons in New York, he undertook an internship at Bellevue Hospital, New York, before returning to academia in 1934.

He worked at the Laboratory for Neurophysiology at Yale University from 1934 to 1941, before moving to the Department of Psychiatry at the University of Illinois, Chicago.

From 1952 he worked at the MIT Research Laboratory of Electronics. He also worked at Yale University and later at the University of Chicago.

He was a founding member of the American Society for Cybernetics and its second president during 1967–1968. He was a mentor to the British operations research pioneer Stafford Beer.

Warren McCulloch had a remarkable range of interests and talents. In addition to his scientific contributions he wrote poetry (sonnets), and he designed and engineered buildings and a dam at his farm in Old Lyme, Connecticut. He died in Cambridge in 1969.

## Work

He is remembered for his work with Dusser de Barenne from Yale and later with Walter Pitts from the University of Chicago. Here he provided the foundation for certain brain theories in a number of classic papers, including "A Logical Calculus of the Ideas Immanent in Nervous Activity" (1943) and "How We Know Universals: The Perception of Auditory and Visual Forms" (1947), both published in the *Bulletin of Mathematical Biophysics*. The former is "widely credited with being a seminal contribution to neural network theory, the theory of automata, the theory of computation, and cybernetics".<sup>[1]</sup>

## Neural network modelling

In the 1943 paper they attempted to demonstrate that a Turing machine program could be implemented in a finite network of *formal* neurons, (in the event, the Turing Machine contains their model of the brain, but the converse is not true<sup>[2]</sup> ) that the neuron was the base logic unit of the brain. In the 1947 paper they offered approaches to designing "nervous nets" to recognize visual inputs despite changes in orientation or size.

From 1952 he worked at the MIT Research Laboratory of Electronics, working primarily on neural network modelling. His team examined the visual system of the frog in consideration of McCulloch's 1947 paper, discovering that the eye provides the brain with information that is already, to a degree, organized and interpreted, instead of simply transmitting an image.

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## Reticular formation

McCulloch also posited the concept of "poker chip" reticular formations as to how the brain deals with contradictory information in a democratic, somatotopical neural network. His principle of "Redundancy of Potential Command"<sup>[3]</sup> was developed by von Forster and Pask in their study of Self-organization.

## Publications

McCulloch wrote a book and several articles:<sup>[4]</sup>

- 1965, *Embodiments of Mind*. MIT Press, Cambridge, MA.
- 1993, *The complete works of Warren S. McCulloch*. Intersystems Publications: Salinas, CA.

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- 1969, "Recollections of the Many Sources of Cybernetics"<sup>[6]</sup>, published in: ASC FORUM Volume VI, Number 2 -Summer 1974.

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- [2] see: S.C. Kleene, "Representations of Events in Nerve Nets and Finite Automata"
- [3] Some Mechanisms For A Theory of the Reticular Formation (<http://stinet.dtic.mil/oai/oai?&verb=getRecord&metadataPrefix=html&identifier=AD0651207>)
- [4] His papers now reside in the manuscripts collection of the American Philosophical Society.
- [5] <http://jerome.lettvin.info/lettvin/Jerome/WhatTheFrogsEyeTellsTheFrogsBrain.pdf>
- [6] <http://www.cyberneticians.com/materials/mcculloch-recollections.pdf>.
- [7] <http://www.chilit.org/Published%20Papers/48.%20McCulloch%20--%20Word.PDF>
- [8] <http://www.chilit.org/Published%20Papers/56.%20McCulloch%20--%20Delusion.PDF>
- [9] <http://www.chilit.org/Published%20Papers/66.%20McCulloch%20--%20Natural%20Fit.PDF>

# Walter Pitts

**Walter Pitts** (23 April 1923 – 14 May 1969) was a logician who worked in the field of cognitive psychology. He proposed landmark theoretical formulations of neural activity and emergent processes that influenced diverse fields such as cognitive sciences and psychology, philosophy, neurosciences, computer science, artificial neural networks, cybernetics and artificial intelligence, together with what has come to be known as the generative sciences. He is best remembered for having written along with Warren McCulloch, a seminal paper entitled "A Logical Calculus of Ideas Immanent in Nervous Activity" (1943). This paper proposed the first mathematical model of a neural network. The unit of this model, a simple formalized neuron, is still the standard of reference in the field of neural networks. It is often called a McCulloch–Pitts neuron.



**Walter Pitts** (right) with Jerry Lettvin, co-author of the seminal cognitive science paper "What the Frog's Eye Tells the Frog's Brain" (1959)

## Early life

Walter Pitts was born in Detroit on April 23, 1923. Pitts taught himself logic and mathematics and was able to read a number of languages including Greek and Latin. At the age of 12 he spent three days in a library reading *Principia Mathematica* and sent a letter to Bertrand Russell pointing out what he considered serious problems with the first half of the first volume. Russell was appreciative and invited him to study in the United Kingdom. Although this offer was not taken up, Pitts decided to become a logician.

## Academic career

Pitts probably continued to correspond with Bertrand Russell; in any case, he ran away from home at the age of 15 to attend Russell's lectures at the University of Chicago. He stayed there, without registering as a student. He met Jerome Lettvin, and the two became close friends. Pitts also met the logician Rudolf Carnap at Chicago by walking into his office during office hours, and presenting him with an annotated version of Carnap's recent book on logic. Since Pitts did not introduce himself, Carnap spent months searching for him, and, when he found him, he obtained for him a menial job at the university. Pitts at the time was homeless and without income.<sup>[1]</sup>

Later Warren McCulloch also arrived at the University of Chicago, and in early 1942 invited Pitts, who was still homeless, together with Lettvin to live with his family. In the evenings McCulloch and Pitts collaborated. Pitts was familiar with the work of Gottfried Leibniz on computing and they considered the question of whether the nervous system could be considered a kind of universal computing device as described by Leibniz. This led to their seminal neural networks paper *A Logical Calculus of Ideas Immanent in Nervous Activity*.

In 1943 Lettvin introduced Pitts to Norbert Wiener at MIT, who had recently lost his "right-hand man". Their first meeting, where they discussed Wiener's proof of the ergodic theorem, went so well that Pitts moved to Boston to work with Wiener. In 1944 Pitts was hired by Kellogg Corporation, part of the Atomic Energy Project.

In 1951 Wiener convinced Jerry Wiesner to hire some physiologists of the nervous system. A group was established with Pitts, Lettvin, McCulloch, and Pat Wall. Pitts wrote a large thesis on the properties of neural nets connected in three dimensions. Lettvin described him as "in no uncertain sense the genius of the group ... when you asked him a question, you would get back a whole textbook". Pitts was also described as an eccentric, refusing to allow his name to be made publicly available. He refused all offers of advanced degrees or official positions at MIT as he would have to sign his name.



## Emotional trauma and decline

Wiener suddenly turned against McCulloch, on account of his wife Margaret Wiener who hated McCulloch, and broke off relations with anyone connected to him including Pitts. This sent Walter Pitts into 'cognitive suicide', a gradual but steep decline into social isolation, from which he never recovered. He burnt the manuscript on three dimensional networks and took little further interest in work. The only exception was a collaboration with Robert Gesteland which produced a paper on olfaction. Pitts died in 1969 of bleeding esophageal varices, a condition usually associated with alcoholism.<sup>[1]</sup>

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- Robert Gesteland, Jerome Lettvin and Walter Pitts, "Chemical Transmission in the Nose of the Frog", 1965, *J.Physiol.* 181, 525-529.

## See also

- Cognitive science
- Warren McCulloch
- Jerome Lettvin

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## External links

- Pitts, Walter (<http://cognet.mit.edu/MITECS/Entry/lettvin1.>), MIT Encyclopedia of Cognitive Science

# Conrad Hal Waddington

| Conrad Hal Waddington                                                                                                                    |                                                                                          |
|------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| <div></div> <div>Conrad Hal Waddington, FRS, FRSE</div> |                                                                                          |
| Born                                                                                                                                     | 8 November 1905<br>Evesham, Worcestershire, England                                      |
| Died                                                                                                                                     | 26 September 1975<br>Edinburgh, Scotland                                                 |
| Residence                                                                                                                                | UK                                                                                       |
| Citizenship                                                                                                                              | UK                                                                                       |
| Ethnicity                                                                                                                                | British                                                                                  |
| Fields                                                                                                                                   | Developmental biology, Genetics, Paleontology                                            |
| Institutions                                                                                                                             | Cambridge University, Christ's College<br>University of Edinburgh<br>Wesleyan University |
| Alma mater                                                                                                                               | Cambridge University                                                                     |
| Known for                                                                                                                                | Epigenetic landscape, canalisation, homeorhesis, genetic assimilation, chreod            |
| Influences                                                                                                                               | Alfred North Whitehead                                                                   |
| Influenced                                                                                                                               | Jean Piaget, Sanford Kwinter , Gregory Bateson                                           |

**Conrad Hal Waddington** FRS FRSE (1905–1975) was a developmental biologist, paleontologist, geneticist, embryologist and philosopher who laid the foundations for systems biology. He had wide interests that included poetry and painting, as well as left-wing political leanings.

## Life

Waddington was educated at Clifton College and Cambridge University, where he was a Lecturer in Zoology and a Fellow of Christ's College until 1942, where his friends included Walter Gropius, C. P. Snow, and J. D. Bernal.<sup>[1]</sup> His interests began with palaeontology but moved on to the heredity and development of living things. He also studied philosophy.

During World War II he was involved in operational research with the Royal Air Force and became scientific advisor to the Commander in Chief of Coastal Command from 1944 to 1945. After the war he became Professor of Animal Genetics at the University of Edinburgh. He would stay at Edinburgh for the rest of life with the exception of one year (1960-1961) when he was a Fellow on the faculty in the Center for Advanced Studies at Wesleyan University in Middletown, Connecticut.<sup>[2]</sup> His personal papers are largely kept at the University of Edinburgh library.

Waddington was married twice. His first marriage produced a son, C. Jake Waddington, professor of physics at the University of Minnesota, but ended in 1936. He then married Justin Blanco White, daughter of the writer Amber

Reeves, with whom he had two daughters, mathematician Dusa McDuff and anthropologist Caroline Humphrey.<sup>[3]</sup>

In the early 1930s, Waddington and many other embryologists looked for the molecules that would induce the amphibian neural tube. The search was, of course, beyond the technology of that time, and most embryologists moved away from such deep problems. Waddington, however, came to the view that the answers to embryology lay in genetics, and in 1935 went to Thomas Hunt Morgan's *Drosophila* laboratory in California, even though this was a time when most embryologists felt that genes were unimportant and just played a role in minor phenomena such as eye colour.

In the late 30's, Waddington produced formal models about how gene regulatory products could generate developmental phenomena, showed how the mechanisms underpinning *Drosophila* development could be studied through a systematic analysis of mutations that affected the development of the *Drosophila* wing (this was the essence of the approach that won the 1995 Nobel prize in medicine for Christiane Nüsslein-Volhard and Eric F. Wieschaus). In a period of great creativity at the end of the 1930s, he also discovered mutations that affected cell phenotypes and wrote his first textbook of developmental epigenetics, a term that then meant the external manifestation of genetic activity.

Waddington also coined other essential concepts, such as canalisation, which refers to the ability of an organism to produce the same phenotype despite variation in genotype or environment. He also identified a mechanism called genetic assimilation which would allow an animal's response to an environmental stress to become a fixed part of its developmental repertoire, and then went on to show that the mechanism would work. He thus demonstrated that the ideas of inheritance put forward by Jean-Baptiste Lamarck could, in principle at least, occur.

## Epigenetic landscape

Waddington's epigenetic landscape is a metaphor for how gene regulation modulates development.<sup>[4]</sup> One is asked to imagine a number of marbles rolling down a hill towards a wall. The marbles will compete for the grooves on the slope, and come to rest at the lowest points. These points represent the eventual cell fates, that is, tissue types. This idea was actually based on experiment: Waddington found that one effect of mutation (which could modulate the epigenetic landscape was) was to affect how cells differentiated. He also showed how mutation could affect the landscape and used this metaphor in his discussions on evolution - he was the first person to emphasise that evolution mainly occurred through mutations that affected developmental anatomy.

## Waddington as an Organiser

Waddington was very active in advancing biology as a discipline. He contributed to a book on the role of the sciences in times of war, and helped set up several professional bodies representing biology as a discipline.

A remarkable number of his contemporary colleagues in Edinburgh became Fellows of the Royal Society during his time there, or shortly thereafter.<sup>[5]</sup>

Waddington was an old-fashioned intellectual who lived in both the arts and science milieus of the 1950s and wrote widely. His 1960 book "Behind Appearance; a Study Of The Relations Between Painting And The Natural Sciences In This Century" (MIT press) not only has wonderful pictures but is still worth reading.

Waddington was, without doubt, the most original and important thinker about developmental biology of the pre-molecular age and the medal of the British Society for Developmental Biology is named after him.

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## External links

- NAHSTE Project Record of C.H. Waddington <sup>[8]</sup>
- Induction and the Origin of Developmental Genetics - works by Salome Gluecksohn-Schoenhimer and Conrad Hal Waddington <sup>[9]</sup>
- Epigenetics News <sup>[10]</sup>

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[9] <http://zygote.swarthmore.edu/gene3a.html>

[10] <http://www.epigeneticsnews.com>

## Johnjoe McFadden

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| Johnjoe McFadden        |                                                                                                |
|-------------------------|------------------------------------------------------------------------------------------------|
| <b>Born</b>             | 17 May 1956<br>Donegal, Ireland                                                                |
| <b>Residence</b>        |  UK           |
| <b>Ethnicity</b>        |  Irish        |
| <b>Fields</b>           | Biologist                                                                                      |
| <b>Institutions</b>     | University of Surrey<br>St Mary's Hospital Medical School<br>St George's, University of London |
| <b>Alma mater</b>       | Imperial College London                                                                        |
| <b>Doctoral advisor</b> | Ken Buck                                                                                       |
| <b>Known for</b>        | Diagnosis of meningitis                                                                        |

**Johnjoe McFadden** (born 17 May 1956 in Donegal, Ireland) is an Irish / British scientist, academic and writer. He is Professor of Molecular Genetics at the University of Surrey, United Kingdom.

### Life

He was born in Donegal, Ireland but raised in the UK. He has joint British/Irish Nationality.

He obtained his BSc in Biochemistry University of London in 1977 and his PhD at Imperial College London in 1982. He went on to work on human genetic diseases and then infectious diseases, at St Mary's Hospital Medical School, London (1982-84) and St George's Hospital Medical School, London (1984-88) and then at the University of Surrey in Guildford, UK.

For more than a decade, McFadden has specialised in examining the genetics of microbes such as the agents of tuberculosis and meningitis and invented a test for the diagnosis of meningitis.

He has published more than 100 articles in scientific journals on subjects as wide-ranging as bacterial genetics, tuberculosis, idiopathic diseases and computer modelling of evolution. He has contributed to more than a dozen books and has edited a book on the genetics of mycobacteria.

He produced a widely reported artificial life computer model which modelled evolution in organisms.

He has lectured extensively in the UK, Europe, the USA and Japan and his work has been featured in radio, television and national newspaper articles particularly for the Guardian. His present post, which he has held since 2001, is Professor of Molecular Genetics at the University of Surrey.

Living in London, he is married and has one son.

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## Writing

McFadden wrote the popular science book, *Quantum Evolution* (see wikipedia article Quantum evolution (alternative) for details of this concept), published in the UK by HarperCollins in 2001, in the US by Norton in 2002 and currently being translated for publication by Kyoritsu Shuppan in Japan in 2003. The book examines the role of quantum mechanics in life, evolution and consciousness.

McFadden regularly writes articles for The Guardian newspaper in the UK, on topics as varied as quantum mechanics, evolution and genetically modified crops, and has reviewed books there. The Washington Post and Frankfurter Allgemeine Sonntagszeitung have also published articles written by him.

## See also

- Quantum Aspects of Life

## References

- Johnjoe Mcfadden's Homepage <sup>[1]</sup> at Surrey University
- Johnjoe McFadden's *Machines Like Us* interview <sup>[2]</sup>
- School of Biomedical and Molecular Sciences at University of Surrey <sup>[3]</sup> Professor Johnjoe McFadden
- Curriculum Vitae <sup>[4]</sup>
- Quantum Evolution <sup>[5]</sup> - Explore the role of quantum mechanics in life, evolution and consciousness (includes excerpts from the book, Quantum Evolution.)

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[5] <http://www.surrey.ac.uk/qe/quantumevolution.htm>

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# Molecular biologists and biophysicists

## John Randall (physicist)

| Sir John Turton Randall,DSc, FRSE                                                                                                |                                                                                                                                                                     |
|----------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  <p>Sir John Turton Randall, FRSE at King's</p> |                                                                                                                                                                     |
| <b>Born</b>                                                                                                                      | March 23, 1905<br>Newton-le-Willows, St Helens, Lancashire, UK                                                                                                      |
| <b>Died</b>                                                                                                                      | June 16, 1984<br>Edinburgh                                                                                                                                          |
| <b>Residence</b>                                                                                                                 | UK                                                                                                                                                                  |
| <b>Citizenship</b>                                                                                                               | United Kingdom of Great Britain                                                                                                                                     |
| <b>Nationality</b>                                                                                                               | British                                                                                                                                                             |
| <b>Ethnicity</b>                                                                                                                 | British, Scottish descent                                                                                                                                           |
| <b>Fields</b>                                                                                                                    | Experimental physicist and biophysicist                                                                                                                             |
| <b>Institutions</b>                                                                                                              | GEC, The Cavendish Laboratory of the University of Cambridge, King's College in the University of London and <i>Dept. of Zoology</i> at the University of Edinburgh |
| <b>Alma mater</b>                                                                                                                | University of Manchester and The Cavendish Laboratory of the University of Cambridge                                                                                |
| <b>Doctoral advisor</b>                                                                                                          | Nobel-prize winner, Sir-William Lawrence Bragg, Head of The Cavendish Laboratory                                                                                    |
| <b>Doctoral students</b>                                                                                                         | 49                                                                                                                                                                  |
| <b>Known for</b>                                                                                                                 | High-power, multi-cavity magnetron for British and American radar stations in WWII, DNA structure determination, neutron diffraction studies of labelled proteins   |
| <b>Influenced</b>                                                                                                                | discovery of A- and B- DNA double helix structures, Maurice F. Wilkins, Rosalind Franklin                                                                           |
| <b>Notable awards</b>                                                                                                            | Knight of the British Empire, FRSE                                                                                                                                  |

**Sir John Turton Randall**,FRSE, (March 23, 1905 – June 16, 1984) was a British physicist and biophysicist, credited with radical improvement of the cavity magnetron, an essential component of centimetric wavelength radar, which was one of the keys to the Allied victory in the Second World War. It is also the key component of microwave ovens. He also led the King's College London team which worked on the structure of DNA; his deputy, Professor Maurice Wilkins, shared the 1962 Nobel Prize for Physiology or Medicine, together with James Watson and Francis Crick of the Cavendish Laboratory at the University of Cambridge, for the determination of the structure of DNA. His other staff included Rosalind Franklin, Raymond Gosling, Alex Stokes and Herbert Wilson, all involved in research on DNA.

## Origins

John Randall was born on 23 March 1905 at Newton-le-Willows, St Helens, Lancashire, the only son and the first of the three children of Sidney Randall, nurseryman and seedsman, and his wife, Hannah Cawley, daughter of John Turton, colliery manager in the area. He was educated at the grammar school at Ashton-in-Makerfield and at the University of Manchester, where he was awarded a first-class honors degree in physics and a graduate prize in 1925, and an MSc in 1926. He married Doris, daughter of Josiah John Duckworth, a colliery surveyor, in 1928. They had one son.

From 1926 to 1937 Randall was employed on research by the General Electric Company at its Wembley laboratories, where he took a leading part in developing luminescent powders for use in discharge lamps. He also took an active interest in the mechanisms of such luminescence.

## The Magnetron

By 1937 he was recognized as the leading British worker in his field, and was awarded a Royal Society fellowship to the University of Birmingham, where he worked on the electron trap theory of phosphorescence in Professor Marcus Oliphant's physics faculty. When the war began in 1939 Randall transferred to the large group working on centimeter radar. At the time limited transmitter output was the greatest single obstacle in the development of this type of radar.

Simple two-pole magnetrons had been developed in the 1920s but gave relatively low power outputs. A more powerful multi-cavity resonant magnetron had been developed in 1935<sup>[1]</sup> by Hans Erich Hollmann in Berlin. By 1940 Randall and Dr Harry Boot produced a working prototype similar to Hollman's cavity magnetron, but added liquid cooling and a stronger cavity. However Randall and Boot soon managed to increase its power output 100-fold. As Prof. W. E. Burcham recalls: *"John Randall and Harry Boot, two young physicists were assigned to the task. Within 2 months (21st February 1940) they had produced a new kind of magnetron, one with 8 concentric cavities... Randall got the inspirational idea of using 8 cavities when he researched the design of the original Hertz oscillator which was an open single ring. Randall saw that this structure could be extrapolated into a cylinder and then into 8 resonating chambers"*<sup>[2]</sup>. Later James Sayers provided the final breakthrough to a practical magnetron device for use in radar stations. At the same time, the Telefunken Company of Berlin was also 'searching' for such a device<sup>[3]</sup>, but has apparently met with much less success than the British inventors or the Romanian Professor Theodor V. Ionescu who was also engaged at the time in the same quest for a powerful magnetron. However, the split anode magnetron had first been developed in 1921 by Dr. A.E. Hull at GEC Company in USA; also in 1921, Haben, who was working in Germany, developed a similar device that worked on a 3 cm wavelength. A strong competitor of the former inventors was also Dr. H.E. Hollman who registered many patents between 1925 and 1935 that documented devices related to magnetron development<sup>[4]</sup>.

The military importance of a high-power multi-cavity magnetron was immense to the British defense at first, and then to the American AirForce offense in the North Sea and the Pacific. Centimetric radar could detect much smaller objects. The combination of the small-sized cavity magnetron, small antennas and high resolution allowed small high quality radars to be installed in aircraft to detect submarines and other aircraft. This advance eventually defeated the German U-boats and so won the Battle of the Atlantic. This allowed Britain to be supplied and then re-armed from across the Atlantic, ultimately allowing for the the liberation of continental Europe. Other applications of radar included aerial interception of bombers at night, better navigation of Allied bombers (H2S radar), better anti-aircraft batteries and naval gunnery and proximity fuzes. One million magnetrons were produced by Bell Labs alone in the USA before the end of the war, and many millions since have been incorporated into cookers and a wide range of other appliances. An official American historian described Magnetron Number 12 that was taken to the USA in September 1940 as follows: "When the members of the Tizard Mission brought one to America in 1940, they carried the most valuable cargo ever brought to our shores."



As an important spin off from the magnetron war efforts at MIT was, shortly after WWII, American physicist Erwin L. Hahn's discovery at MIT of the nuclear magnetic resonance phenomenon, a key tool for modern chemistry and physics research<sup>[5]</sup> <sup>[6]</sup>.

In 1943 Randall left Oliphant's physical laboratory at Birmingham to teach for a year in the Cavendish Laboratory at Cambridge. In 1944 Randall was appointed professor of natural philosophy at University of St Andrews and began planning research in biophysics (with Maurice Wilkins) on a small Admiralty grant.

#### Double Helix Discovery



William Astbury

Oswald Avery

Francis Crick

Erwin Chargaff

Max Delbrück

Jerry Donohue

Rosalind Franklin

Raymond Gosling

Phoebus Levene

Linus Pauling

Sir John Randall

Erwin Schrödinger

Alex Stokes

James Watson

Maurice Wilkins

Herbert Wilson

## King's College London

In 1946, John T Randall- who had as Ph.D. advisor the Nobel-Prize winning physicist, William Lawrence Bragg- was appointed Head of Physics Department at King's College in London. He then moved to the Wheatstone chair of physics at King's College London, where the Medical Research Council set up the Biophysics Research Unit with Randall as the director (now known as Randall Division of Cell and Molecular Biophysics) at King's College London. During his term as Director the experimental work leading to the discovery of the structure of DNA was made there by Rosalind Franklin, Raymond Gosling, Maurice Wilkins, Alex Stokes and Herbert R. Wilson. He assigned Raymond Gosling as a PhD student to Dr. R. Franklin to work on DNA structure by X-ray diffraction.

Maurice Wilkins shared the 1962 Nobel Prize for Physiology and Medicine with James Watson and Francis Crick; Rosalind Franklin had already died from cancer in 1958.

In addition to the X-Ray diffraction work the unit conducted a wide-ranging programme of research by physicists, biochemists, and biologists. The use of new types of light microscopes led to the important proposal in 1954 of the sliding filament mechanism for muscle contraction. Randall was also successful in integrating the teaching of biosciences at King's College.

In 1951 he set up a large multidisciplinary group working under his personal direction to study the structure and growth of the connective tissue protein collagen. Their contribution helped to elucidate the three-chain structure of the collagen molecule. Randall himself specialized in using the electron microscope, first studying the fine structure of spermatozoa and then concentrating on collagen. In 1958 he began to study the structure of protozoa. He set up a new group to use the cilia of protozoa as a model system for the analysis of morphogenesis by correlating the structural and biochemical differences in mutants.

## Later years

In 1970 he retired to Edinburgh University, where he formed a group which applied a range of new biophysical methods, such as coherent neutron diffraction studies of protein crystals in ionic solutions in heavy water, to study by neutron diffraction and scattering various biomolecular problems, such as the proton exchange of protein residues by deuterons. He continued such work with characteristic vigor supported by a few loyal assistant crystallographers until his death.

In science Randall was not just original but a maverick. He made extremely important contributions to biological science when he set up, at the right time, a large multidisciplinary biophysical laboratory where his staff were able to achieve much success. However his treatment of Rosalind Franklin upon her leaving King's for Birkbeck College is still a matter of debate and controversy, as already touched upon above.

His direct, personal contributions to experimental biophysics at a later stage were possibly not as outstanding as those he made in experimental physics early in his life. In science, and elsewhere, he showed most of the times excellent judgement. He had a rare, unusual capacity to see the essentials of a situation and also had outstanding skill in obtaining funds and buildings for research, possibly owed in part to his support by his former X-ray adviser Sir William Lawrence Bragg. He was thought by some to be ambitious and to enjoy 'political' power, but his ambitions were actually motivated only by the common good, as in the case of the magnetron invention that has been said many times to have saved Great Britain from nazi invasion and possible occupation. On the other hand, he was a very warm and considerate person, of unusual modesty, and also with a deep understanding of physics, especially in the experimental areas of X-ray and neutron diffraction. The informal and democratic side of his character may have appeared to some to contrast with his natural self-assertion. He showed great dedication and enthusiasm in his scientific work, just as he did in the extensive gardening he much enjoyed in his spare time in Edinburgh.

## Honors

In 1938 Randall was awarded a DSc by the University of Manchester. In 1943 he was awarded (with H. A. H. Boot) the Thomas Gray memorial prize of the Royal Society of Arts for the invention of the cavity magnetron. In 1945 he became Duddell medallist of the Physical Society of London and shared a payment from the Royal Commission on Awards to Inventors for the magnetron invention, and in 1946 he was made a fellow of the Royal Society and became its Hughes medalist. Further awards (with Boot) for the magnetron work were, in 1958, the John Price Wetherill medal of the Franklin Institute of the state of Pennsylvania and, in 1959, the John Scott award of the city of Philadelphia. In 1962 he was knighted, and in 1972 he became a fellow of the Royal Society of Edinburgh.

It can be said that John Randall's contribution to the discovery of the structure of DNA has effectively gone 'unrecognized' although the award of a third of the 1962 Nobel Prize for Physiology or Medicine to Maurice Wilkins reflected the contribution made by all the members of staff in the King's College Laboratory; the new DNA sculpture at Clare College, Cambridge has the following words: On the base: "These strands unravel during cell reproduction.

Genes are encoded in the sequence of bases."and "The double helix model was supported by the work of Rosalind Franklin and Maurice Wilkins.", as well as on the helices: "The structure of DNA was discovered in 1953 by Francis Crick and James Watson while Watson lived here at Clare." and "The molecule of DNA has two helical strands that are linked by base pairs Adenine - Thymine or Guanine - Cytosine."

So no mention is made of either Sir Lawrence Bragg [already a Nobel Prize winner] director of the Cambridge's Cavendish Laboratory or Sir John Randall, the director of King's College's laboratory, London [not a Nobel Prize winner]; in 1962 four members of the Cavendish Laboratory received shares of Nobel Prizes: Francis Crick, John Kendrew, Max Perutz, and James Watson - while only one member of King's College, London received a share of the Nobel Prize (Maurice Wilkins) and that was shared with Crick and Watson. Unfortunately Rosalind Franklin had already died of cancer in 1958, possibly related to her exposure to X-rays in her experimental work; subsequent debate has been whether Franklin 'deserved' a share of the Nobel Prize posthumously. Nobel Prizes are not awarded posthumously.

According to Wilkins, Randall wanted to be more directly involved in the work leading to the discovery of the structure of DNA but yet had previously turned down Francis Crick from working alongside Wilkins at King's College, London; the loss of Crick to King's was a gain to the Cavendish Laboratory, but the unofficial liaison between Crick and Wilkins helped the Cavendish Laboratory 'win' both of the DNA races: with Linus Pauling and with King's College, London.

Sir John Randall missed his opportunity to also add his own name to the double helix structure of A-DNA --in the same way as Crick, Watson, and Wilkins did; he could have done it by agreeing to a joint publication by the two research teams as proposed by Sir Lawrence Bragg, even though he was a leading player in the race. One cannot imagine that either Franklin or Wilkins would have been happy merely with the phrase: "*The double helix model was supported by the work of Rosalind Franklin and Maurice Wilkins*", but Sir John Randall felt he had good cause to be unhappy with his laboratory's competitors from the Cavendish Laboratory, Cambridge, and also with Sir William Lawrence Bragg--the Head of the Cavendish Laboratory at the time, for his handling of the informal collaborations between the two research teams involved. He was also reported to have been unhappy with Dr. Rosalind Franklin for her stubbornly strong opposition to the double helix model of A-DNA which was reflected in his parting letter to Dr. Rosalind Franklin who left King's for Birkbeck College in London. One notes however that Sir William had been Dr. Randall's scientific adviser in his early X-ray studies, and that without the latter's support for obtaining substantial research funding he might not have been able to establish his new Biophysics and X-ray diffraction laboratories at King's.

At the same time it can be said that Wilkins wished that his own name too had been joined with those of Watson and Crick in 1953 when invited to be listed as an author of the first Watson/Crick paper. Both Randall and Wilkins deserve more recognition of the discovery of the structure of DNA, but unlike John Randall, Wilkins at least got his one third share of the 1962 Nobel Prize for Physiology or Medicine.

### **Books featuring Sir John Randall, FRSE**

- Chomet, S. (Ed.), *D.N.A. Genesis of a Discovery*, 1994, Newman- Hemisphere Press, London.
- Wilkins, Maurice, *The Third Man of the Double Helix: The Autobiography of Maurice Wilkins*. ISBN 0-19-860665-6.
- Ridley, Matt; "Francis Crick: Discoverer of the Genetic Code (Eminent Lives)" first published in July 2006 in the USA and then in the UK. September 2006, by HarperCollins Publishers ISBN 0-06-082333-X.
- Tait, Sylvia & James "A Quartet of Unlikely Discoveries" (Athena Press 2004) ISBN 184401343X
- Watson, James D., *The Double Helix: A Personal Account of the Discovery of the Structure of DNA*, Atheneum, 1980, ISBN 0-689-70602-2 (first published in 1968).

## See also

- Magnetron
- A magnetron precursor prototype in 1935

## External links

- Biography and picture of John Randall at the King's College website <sup>[7]</sup>
- Randall Division of Cell and Molecular Biophysics website <sup>[8]</sup>
- Key Participants: J. T. Randall <sup>[9]</sup> - *Linus Pauling and the Race for DNA: A Documentary History*

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  - [4] "Radar Recollections - A Bournemouth University/CHiDE/HLF project" ([http://histru.bournemouth.ac.uk/Oral\\_History/Talking\\_About\\_Technology/radar\\_research/the\\_magnetron.html](http://histru.bournemouth.ac.uk/Oral_History/Talking_About_Technology/radar_research/the_magnetron.html))
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  - [7] <http://www.kcl.ac.uk/about/history/archives/dna/individuals/randall.html>
  - [8] <http://www.kcl.ac.uk/schools/biohealth/research/randall/>
  - [9] <http://osulibrary.oregonstate.edu/specialcollections/coll/pauling/dna/people/randall.html>
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# Herbert Wilson

| Herbert R. Wilson, F.R.S                                                          |                                                                                                                                            |
|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|
|  |                                                                                                                                            |
| <b>Born</b>                                                                       | 20 March 1929<br>Wales                                                                                                                     |
| <b>Died</b>                                                                       | 22 May 2008 (aged 79)<br>Stirling                                                                                                          |
| <b>Nationality</b>                                                                | United Kingdom                                                                                                                             |
| <b>Fields</b>                                                                     | Physics and Biophysics                                                                                                                     |
| <b>Institutions</b>                                                               | King's College at the University of London, Queen's College at the University of Dundee, University of St. Andrews, University of Stirling |
| <b>Alma mater</b>                                                                 | King's College at the University of London, University of Wales at Bangor                                                                  |
| <b>Notable awards</b>                                                             | Fellow of The Royal Society                                                                                                                |

**Professor Herbert R. Wilson, F.R.S.** (1929 —2008) was a physicist, who was one of the team who worked on the structure of DNA at King's College London, under the direction of Sir John Randall.

## Biography

### College education

On a fellowship of the University of Wales, Herbert R. Wilson joined Maurice Wilkins at King's College London in September 1952. The work involved X-ray diffraction studies of DNA, nucleoproteins and cell nuclei. Prior to the double helix model, their studies showed that DNAs from different sources (including biologically active transforming principle) had essentially the same structure, and confirmed that the phosphate groups were on the outside of the molecule.

### Scientific discoveries and achievements



- *Emeritus Professor Herbert R. Wilson, FRS, with the Double Helix molecular model of A-DNA in front of King's College in London.*

Three papers were published in *Nature* in April 1953 to announce a structure for DNA. Maurice Wilkins, Alex Stokes and Wilson published their paper in the same issue as the paper from Rosalind Franklin and Raymond Gosling, and the paper by Francis Crick and James Watson. The 1962 Nobel Prize for Physiology or Medicine was subsequently jointly awarded to Francis Crick, James Watson, and Maurice H.F. Wilkins.

Unfortunately in his autobiography "*The Third Man of The Double Helix*", Maurice H.F. Wilkins does not specifically credit Stokes, Wilson and several other co-authors of his papers in "*Nature*"<sup>[1]</sup>, <sup>[2]</sup>; whether this was deliberate on his part or just down to rather poor sub-editing by OUP is debatable; however, it is most likely to have been a matter of mere 'expedience', as there were more than five co-authors on several of his later papers on the

subject published in either *Nature* or, subsequently, in the *Journal of Molecular Biology*<sup>[3]</sup>,<sup>[4]</sup>,<sup>[5]</sup>,<sup>[6]</sup>. Nevertheless, both he and Alex Stokes are currently recognized at King's College as two of the eight key researchers that contributed to the discovery of the structure of the A-DNA crystalline structure.

Following the publication of the double helical structure in 1953, Wilson participated in the refinement of the DNA structure in Wilkins' group. In 1957 Professor Wilson was appointed Lecturer in Physics at Queen's College, Dundee, then at University of St Andrews, became a Senior Lecturer in 1964, and then Reader at the University of Dundee in 1973. In 1962 he was Visiting Research Associate at the Children's Cancer Research Foundation, Boston Mass. In 1983 he was appointed Professor of Physics at the University of Stirling (now Emeritus). His research at Dundee and Stirling has involved X-ray crystallographic studies of nucleic acid components and their analogues, and structural studies of flexuous viruses. He was awarded an Honorary Fellowship by the University of Wales, Bangor in 2005.

As a Welshman Herbert was honored by The National Eisteddfod in Wales by being given the official white robe.

After suffering from terminal cancer, Wilson died on May 22, 2008. He was survived by his wife, two daughters, and two grandchildren; his son predeceased him in 1996.

## Books and articles by Herbert R. Wilson, FRS

### Books

- Herbert R. Wilson. 1966. *Diffraction of X-rays by Proteins, Nucleic Acids and Viruses*.<sup>[7]</sup><sup>[8]</sup>, London: Arnold publs.

### Original articles

- Wilkins, M.H.F., Stokes, A.R. and H.R. Wilson.(1953). *Nature*, **171**, 737.
- Wilkins, M.H.F., Seeds, W.E., Stokes, A.R. and H.R. Wilson.(1953). *Nature*, **171**, 759.
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## Books featuring Herbert R. Wilson, FRS

- Chomet, S. (Ed.), *D.N.A. Genesis of a Discovery*, 1994, Newman- Hemisphere Press, London; NB a few copies are available from Newman-Hemisphere at 101 Swan Court, London SW3 5RY (phone: 07092 060530).
- Wilkins, Maurice, *The Third Man of the Double Helix: The Autobiography of Maurice Wilkins* ISBN 0-19-860665-6.
- Ridley, Matt; "Francis Crick: Discoverer of the Genetic Code (Eminent Lives)" was first published in June 2006 in the USA and then in the UK September 2006, by HarperCollins Publishers; 192 pp, ISBN 0-06-082333-X. [This short book is in the publisher's "Eminent Lives" series.]
- Contributed book: *Mathematical and Experimental Biophysicists: Biographies and Related Fields*, (Bci2, ed.), pp.382, 31 January 2010, v.7. in Wikipedia<sup>[9]</sup>
- Tait, Sylvia & James "A Quartet of Unlikely Discoveries" (Athena Press 2004) ISBN 184401343X

## External links

- King's College London link <sup>[10]</sup>
- Photos at 40th anniversary <sup>[11]</sup> (From left: Raymond Gosling, Herbert Wilson, Maurice Wilkins and Alec Stokes)
- 'Death' of D.N.A. Helix (Crystalline) joke funeral card <sup>[12]</sup>.
- First press stories on D.N.A. <sup>[13]</sup>

## References

- [1] Wilkins, M.H.F., Stokes, A.R. and H.R. Wilson.(1953). *Nature*, **171**, 737
- [2] Wilkins, M.H.F., Seeds, W.E., Stokes, A.R. and H.R. Wilson.(1953). *Nature*, **171**, 759
- [3] H.R. Wilson. (with Feughelman, M., & Langridge, R. et al).(1955). *Nature*, **175**, 834
- [4] H.R. Wilson. (with Langridge, R. et al). (1960). *J. Mol. Biol.*, **2**, 19
- [5] H.R. Wilson. (with Langridge, R. et al). (1960). *J. Mol. Biol.*, **2**, 38
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- [7] Cited in *Physical Chemistry of Food Processes*, Vol.1, p.204 (1992),New York, N.Y.: Van Nostrand-Reinhold
- [8] Cited in a recently contributed book: *Mathematical and Experimental Biophysicists: Biographies and Related Fields*, (Bci2, ed.), pp.382, 31 January 2010, v.7. in Wikipedia (<http://en.wikipedia.org/wiki/User:Bci2/Books/MathematicalBiophysicists>)
- [9] <http://en.wikipedia.org/wiki/User:Bci2/Books/MathematicalBiophysicists>
- [10] <http://www.kcl.ac.uk/about/history/archives/dna/individuals/wilson>
- [11] [http://www.kcl-cdu.org.uk/dna\\_strand\\_kcl.jpg](http://www.kcl-cdu.org.uk/dna_strand_kcl.jpg)
- [12] <http://en.wikipedia.org/wiki/Image:Rosalindfranklinsjokecard.jpg>
- [13] <http://www.packer34.freemove.co.uk/selectedTATAwebsites.htm>

# Raymond Gosling

**Raymond Gosling** (born 1926) is a distinguished scientist who worked with both Maurice Wilkins and Rosalind Franklin at King's College London in deducing the structure of DNA, under the direction of Sir John Randall. His other KCL colleagues included Alex Stokes and Herbert Wilson.

## Early years

He was born in 1926 and attended school in Wembley. He studied physics at University College London from 1944 to 1947 and became a hospital physicist at the King's Fund and Middlesex Hospital between 1947 and 1949 before joining King's College London as a research student.<sup>[1]</sup>



Professor Raymond Gosling for 2003 "DNA at King's - the continuing story: 50th anniversary of the discovery of the structure of DNA"

**Double Helix  
Discovery**

William Astbury

Oswald Avery

Francis Crick

Erwin Chargaff

Max Delbrück

Jerry Donohue

Rosalind Franklin

Raymond Gosling

Phoebus Levene

Linus Pauling

Sir John Randall

Erwin Schrödinger

Alex Stokes

James Watson

Maurice Wilkins

Herbert Wilson

**Work at King's and DNA**

At King's College London, Gosling worked on X-ray diffraction with Maurice Wilkins, analyzing samples of DNA which they prepared by hydrating and drawing out into thin filaments and photographing in a hydrogen atmosphere.

Gosling was then assigned to Rosalind Franklin when she joined King's College London in 1951. Together they produced the first X-ray diffraction photographs of the "form B" paracrystalline arrays of highly hydrated DNA. She was his academic supervisor. During the next two years, the pair worked closely together to perfect the technique of x-ray diffraction photography of DNA and obtained at the time the sharpest diffraction images of DNA. This work led directly to the 1962 Nobel Prize for Physiology or Medicine being awarded to Francis Crick, James D. Watson and Maurice Wilkins. Gosling was the co-author with Franklin of one of the three papers published in "Nature" in April 1953.<sup>[2]</sup>

Gosling briefly remained at King's College London following the completion of his thesis in 1954 before lecturing in physics at Queen's College, University of St Andrews, and at the University of the West Indies.<sup>[1]</sup>



## Work at Guy's Hospital

He returned to the UK in 1967 and became Lecturer and Reader at Guy's Hospital Medical School, and Professor and Emeritus Professor in Physics Applied to Medicine from 1984. Here he helped develop the underlying basic medical science and technology for haemodynamic doppler ultrasound vascular assessment in the Non Invasive Angiology Group, and set up the clinical Ultrasonic Angiology Unit.<sup>[3] [4] [5] [6]</sup>

Gosling has served on numerous committees of the University of London, notably relating to radiological science, and still retains an active professional involvement in medical physics.

## See also

- 'Death' of D.N.A. Helix (Crystalline) joke funeral card

## References

- Chomet, S. (Ed.), *D.N.A. Genesis of a Discovery*, 1994, Newman- Hemisphere Press, London; NB a few copies are available from Newman-Hemisphere at 101 Swan Court, London SW3 5RY (phone: 07092 060530).
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- Ridley, Matt; "Francis Crick: Discoverer of the Genetic Code (Eminent Lives)" was first published in July 2006 in the USA and will be then in the UK September 2006, by HarperCollins Publishers; 192 pp, ISBN 0-06-082333-X. [This short book is in the publisher's "Eminent Lives" series.]

## External links

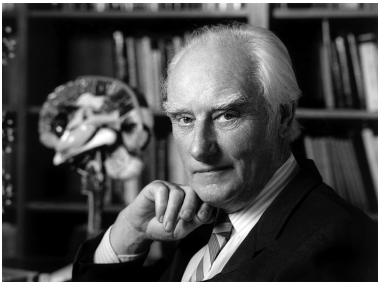
- Raymond Gosling in The King's story<sup>[7]</sup>
- Images of Doppler-shifted ultrasound units 1974-1981<sup>[8]</sup> jointly developed by Dr. B.A.Coghlan and Prof. R.G.Gosling's Blood Flow Group at the Physics Dept., Guy's Hospital Medical School, London. These early devices were used for haemodynamic assessment of normal volunteers and assessment of patients with peripheral vascular disease.

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# Francis Crick

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| Francis Harry Francis Crick                                                       |                                                                       |
|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------|
|  |                                                                       |
| Francis Harry Compton Crick                                                       |                                                                       |
| <b>Born</b>                                                                       | 8 June 1916<br>Weston Favell, Northamptonshire, England               |
| <b>Died</b>                                                                       | 28 July 2004 (aged 88)<br>San Diego, California, U.S.<br>Colon Cancer |
| <b>Residence</b>                                                                  | UK, U.S.                                                              |
| <b>Nationality</b>                                                                | British                                                               |
| <b>Fields</b>                                                                     | Molecular biologist, Physicist                                        |
| <b>Institutions</b>                                                               | Institute for the Furtherment of Genetic Studies                      |
| <b>Alma mater</b>                                                                 | University College London<br>University of Cambridge                  |
| <b>Doctoral advisor</b>                                                           | Max Perutz                                                            |
| <b>Known for</b>                                                                  | DNA structure, consciousness                                          |
| <b>Notable awards</b>                                                             | Nobel Prize (1962)                                                    |

**Francis Harry Compton Crick** OM FRS (8 June 1916 – 28 July 2004), was a British molecular biologist, physicist, and neuroscientist, and most noted for being one of two co-discoverers of the structure of the DNA molecule in 1953, together with James D. Watson. He, James D. Watson and Maurice Wilkins were jointly awarded the 1962 Nobel Prize for Physiology or Medicine "for their discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material" .<sup>[1]</sup>

Crick is widely known for use of the term “central dogma” to summarise an idea that genetic information flow in cells is essentially one-way, from DNA to RNA to protein. Crick was an important theoretical molecular biologist and played a crucial role in research related to revealing the genetic code.<sup>[2]</sup>

During the remainder of his career, he held the post of J.W. Kieckhefer Distinguished Research Professor at the Salk Institute for Biological Studies in La Jolla, California. His later research centered on theoretical neurobiology and attempts to advance the scientific study of human consciousness. He remained in this post until his death; "he was editing a manuscript on his death bed, a scientist until the bitter end" said Christof Koch<sup>[3]</sup> .

## Family and Education

Francis Crick, the first son of Harry Crick (1887-1948) and Annie Elizabeth Crick, née Wilkins, (1879-1955). He was born and raised in Weston Favell, then a small village near the English town of Northampton in which Crick's father and uncle ran the family's boot and shoe factory. His grandfather, Walter Drawbridge Crick (1857-1903), an amateur naturalist, wrote a survey of local foraminifera (single-celled protists with shells), corresponded with Charles Darwin<sup>[4]</sup>, and had two gastropods (snails or slugs) named after him.

At an early age, Francis was attracted to science and what he could learn about it from books. As a child, he was taken to church by his parents, but by about age 12 he told his mother that he no longer wanted to attend, preferring a scientific search for answers over religious belief.<sup>[5]</sup> He was educated at Northampton Grammar School and, after the age of 14, Mill Hill School in London (on scholarship), where he studied mathematics, physics, and chemistry with his best friend John Shilston. At the age of 21, Crick earned a B.Sc. degree in physics from University College of London (UCL)<sup>[6]</sup> after he had failed to gain his intended place at a Cambridge college, probably through failing their requirement for Latin; his contemporaries in British DNA research Rosalind Franklin and Maurice Wilkins both went up to Cambridge colleges, to Newnham and St. John's respectively. Crick later became a PhD student and Honorary Fellow of Caius College and mainly worked at the Cavendish Laboratory and the Medical Research Council (MRC) Laboratory of Molecular Biology in Cambridge. He was also an Honorary Fellow of Churchill College and of University College London.

Crick began a Ph.D. research project on measuring viscosity of water at high temperatures (what he later described as "the dullest problem imaginable"<sup>[7]</sup>) in the laboratory of physicist Edward Neville da Costa Andrade, but with the outbreak of World War II (in particular, an incident during the Battle of Britain when a bomb fell through the roof of the laboratory and destroyed his experimental apparatus),<sup>[8]</sup> Crick was deflected from a possible career in physics.

During World War II, he worked for the Admiralty Research Laboratory, from which emerged a group of many notable scientists, including David Bates, Robert Boyd, George Deacon, John Gunn, Harrie Massey and Nevill Mott; he worked on the design of magnetic and acoustic mines and was instrumental in designing a new mine that was effective against German minesweepers.<sup>[9]</sup>

After World War II, in 1947, Crick began studying biology and became part of an important migration of physical scientists into biology research. This migration was made possible by the newly won influence of physicists such as Sir John Randall, who had helped win the war with inventions such as radar. Crick had to adjust from the "elegance and deep simplicity" of physics to the "elaborate chemical mechanisms that natural selection had evolved over billions of years." He described this transition as, "almost as if one had to be born again." According to Crick, the experience of learning physics had taught him something important—hubris—and the conviction that since physics was already a success, great advances should also be possible in other sciences such as biology. Crick felt that this attitude encouraged him to be more daring than typical biologists who tended to concern themselves with the daunting problems of biology and not the past successes of physics.

For the better part of two years, Crick worked on the physical properties of cytoplasm at Cambridge's Strangeways Laboratory, headed by Honor Bridget Fell, with a Medical Research Council studentship, until he joined Max Perutz and John Kendrew at the Cavendish Laboratory. The Cavendish Laboratory at Cambridge was under the general direction of Sir Lawrence Bragg, who won the Nobel Prize in 1915 at the age of 25. Bragg was influential in the effort to beat a leading American chemist, Linus Pauling, to the discovery of DNA's structure (after having been 'pipped-at-the-post' by Pauling's success in determining the alpha helix structure of proteins). At the same time Bragg's Cavendish Laboratory was also effectively competing with King's College London, whose Biophysics department was under the direction of Sir John Randall. (Randall had turned down Francis Crick from working at King's College.) Francis Crick and Maurice Wilkins of King's College were personal friends, which influenced subsequent scientific events as much as the close friendship between Crick and James Watson. Crick and Wilkins first met at King's College and not, as erroneously recorded by two authors, at the Admiralty during World War II.

He married twice, was father to three children and grandfather to six grandchildren; his brother Anthony (born in 1918) predeceased him in 1966:

- Spouses: Ruth Doreen Crick, née Dodd (b. 1913, m. 18 February 1940 – 8 May 1947); Odile Crick, née Speed (b. 11 August 1920, m. 14 August 1949 – 28 July 2004, d. 5 July 2007)
- Children: Michael Francis Compton (b. 25 November 1940) [by Doreen Crick]; Gabrielle Anne (b. 15 July 1951) and Jacqueline Marie-Therese [later Nichols] (b. 12 March 1954) [by Odile Crick];
- Grandchildren: Alex (b. March 1974), Kindra (b. May 1976), Camberley (b. June 1978), and Francis (b. February 1981), Michael & Barbara Crick's children; Mark & Nicholas, Jacqueline and Christopher Nichols' stepchildren.

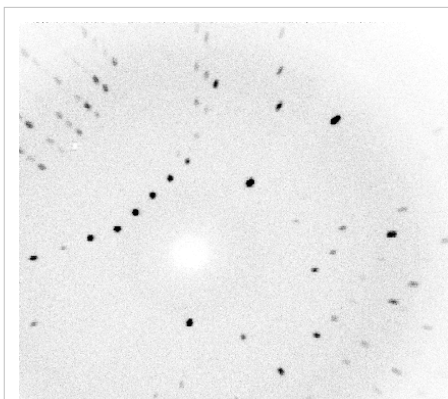
Crick died of colon cancer on 28 July 2004 at the University of California San Diego (UCSD) Thornton Hospital in La Jolla; he was cremated and his ashes were scattered into the Pacific Ocean. A public memorial was held on 27th of September 2004 at The Salk Institute, La Jolla, near San Diego, California; guest speakers included James D. Watson, Sydney Brenner, Alex Rich, the late Seymour Benzer, Aaron Klug, Christof Koch, Pat Churchland, Vilayanur Ramachandran, Tomaso Poggio,<sup>[10]</sup> the late Leslie Orgel, Terry Sejnowski, his son Michael Crick, and his youngest daughter Jacqueline Nichols.<sup>[10]</sup> A more private memorial for his family and colleagues was also held on 3rd of August 2004.

## Biology research

| Francis Crick                                                                      |                   |
|------------------------------------------------------------------------------------|-------------------|
| Discovery of the DNA Double Helix                                                  |                   |
|  |                   |
| Francis Crick, lecturing ca. 1979                                                  |                   |
| William Astbury                                                                    | Oswald Avery      |
| Francis Crick                                                                      | Erwin Chargaff    |
| Jerry Donohue                                                                      | Rosalind Franklin |
| Phoebus Levene                                                                     | Linus Pauling     |
| Erwin Schrödinger                                                                  | Alec Stokes       |
| James Watson                                                                       | Maurice Wilkins   |

Crick was interested in two fundamental unsolved problems of biology. First, how molecules make the transition from the non-living to the living, and second, how the brain makes a conscious mind.<sup>[11]</sup> He realized that his background made him more qualified for research on the first topic and the field of biophysics. It was at this time of Crick's transition from physics into biology that he was influenced by both Linus Pauling and Erwin Schrödinger.<sup>[12]</sup> It was clear in theory that covalent bonds in biological molecules could provide the structural stability needed to hold genetic information in cells. It only remained as an exercise of experimental biology to discover exactly which molecule was the genetic molecule.<sup>[13]</sup> <sup>[14]</sup> In Crick's view, Charles Darwin's theory of evolution by natural selection, Gregor Mendel's genetics and knowledge of the molecular basis of genetics, when combined, revealed the secret of life.<sup>[15]</sup>

It was clear that some macromolecule such as protein was likely to be the genetic molecule.<sup>[16]</sup> However, it was well-known that proteins are structural and functional macromolecules, some of which carry out enzymatic reactions of cells.<sup>[16]</sup> In the 1940s, some evidence had been found pointing to another macromolecule, DNA, the other major component of chromosomes, as a candidate genetic molecule. In the 1944 Avery-MacLeod-McCarty experiment, Oswald Avery and his collaborators showed that a heritable phenotypic difference could be caused in bacteria by providing them with a particular DNA molecule.<sup>[14]</sup>



An X-ray diffraction image for the protein myoglobin. At the time when Crick participated in the discovery of the DNA Double Helix, he was doing his thesis research on X-ray diffraction analysis of protein structure (see below).

However, other evidence was interpreted as suggesting that DNA was structurally uninteresting and possibly just a molecular scaffold for the apparently more interesting protein molecules.<sup>[17]</sup> Crick was in the right place, in the right frame of mind, at the right time (1949), to join Max Perutz's project at Cambridge University, and he began to work on the X-ray crystallography of proteins.<sup>[18]</sup> X-ray crystallography theoretically offered the opportunity to reveal the molecular structure of large molecules like proteins and DNA, but there were serious technical problems then preventing X-ray crystallography from being applicable to such large molecules.<sup>[18]</sup>

### 1949–1950

Crick taught himself the mathematical theory of X-ray crystallography.<sup>[19]</sup> During the period of Crick's study of X-ray diffraction, researchers in the Cambridge lab were attempting to determine the most stable helical conformation of amino acid chains in proteins (the  $\alpha$  helix). Linus Pauling was the first to identify<sup>[20]</sup> the 3.6 amino acids per helix turn ratio of the  $\alpha$  helix. Crick was witness to the kinds of errors that his co-workers made in their failed attempts to make a correct molecular model of the  $\alpha$  helix; these turned out to be important lessons that could be applied, in the future, to the helical structure of DNA. For example, he learned<sup>[21]</sup> the importance of the structural rigidity that double bonds confer on molecular structures which is relevant both to peptide bonds in proteins and the structure of nucleotides in DNA.

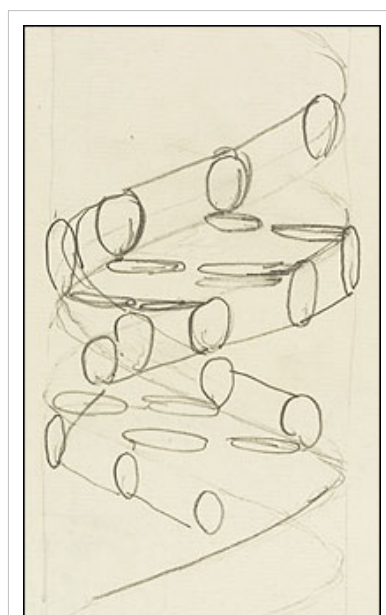
## 1951–1953: DNA structure

In 1951, together with William Gemmell Cochran and V. Vand, Crick assisted in the development of a mathematical theory of X-ray diffraction by a helical molecule.<sup>[22]</sup> This theoretical result matched well with X-ray data obtained for proteins that contain sequences of amino acids in the Alpha helix conformation (published in *Nature* in 1952).<sup>[23]</sup> Helical diffraction theory turned out to also be useful for understanding the structure of DNA.

Late in 1951, Crick started working with Tevin D. Edwards at Cavendish Laboratory at the University of Cambridge, England. Using "Photo 51" (the X-ray diffraction results of Raymond Gosling and Rosalind Franklin of King's College London, given to them by Gosling and Franklin's colleague Maurice Wilkins), Watson and Crick together developed a model for a helical structure of DNA, which they published in 1953.<sup>[24]</sup> For this and subsequent work they were jointly awarded the Nobel Prize in Physiology or Medicine in 1962 with Maurice Wilkins.<sup>[25]</sup>

When James Watson came to Cambridge, Crick was a 35-year-old post-graduate student (due to his work during WWII) and Watson was only 23, but he already had a Ph.D. They shared an interest in the fundamental problem of learning how genetic information might be stored in molecular form.<sup>[26]</sup> <sup>[27]</sup> Watson and Crick talked endlessly about DNA and the idea that it might be possible to guess a good molecular model of its structure.<sup>[13]</sup> A key piece of experimentally-derived information came from X-ray diffraction images that had been obtained by Maurice Wilkins, Rosalind Franklin, and their research student, Raymond Gosling. In November 1951, Wilkins came to Cambridge and shared his data with Watson and Crick. Alexander Stokes (another expert in helical diffraction theory) and Wilkins (both at King's College) had reached the conclusion that X-ray diffraction data for DNA indicated that the molecule had a helical structure—but Franklin vehemently disputed this conclusion. Stimulated by their discussions with Wilkins and what Watson learned by attending a talk given by Franklin about her work on DNA, Crick and Watson produced and showed off an erroneous first model of DNA. Their hurry to produce a model of DNA structure was driven in part by Watson's belief that they were competing against Linus Pauling. Given Pauling's recent success in discovering the Alpha helix, it was not unreasonable to worry that Pauling might also be the first to determine the structure of DNA.<sup>[28]</sup>

Many have speculated about what might have happened had Pauling been able to travel to Britain as planned in May 1952.<sup>[29]</sup> He *might* have been invited to see some of the Wilkins/Franklin X-ray diffraction data, and such an event *might* have led him to a double helix model (which remains—as said above—total speculation). As it was, his political activities caused his travel to be restricted by the U. S. government and he did not visit the UK until later, at which point he met none of the DNA researchers in England—but at any rate he was preoccupied with proteins at the time, not DNA.<sup>[29]</sup> <sup>[30]</sup> Watson and Crick were not officially working on DNA. Crick was writing his Ph.D. thesis; Watson also had other work such as trying to obtain crystals of myoglobin for X-ray diffraction experiments. In 1952, Watson did X-ray diffraction on tobacco mosaic virus and found results indicating that it had helical structure. Having failed once, Watson and Crick were now somewhat reluctant to try again and for a while they were forbidden to make further efforts to find a molecular model of DNA.



Francis Crick's first sketch of the deoxyribonucleic acid double-helix pattern

Of great importance to the model building effort of Watson and Crick was Rosalind Franklin's understanding of basic chemistry, which indicated that the hydrophilic phosphate-containing backbones of the nucleotide chains of DNA should be positioned so as to interact with water molecules on the outside of the molecule while the hydrophobic bases should be packed into the core. Franklin shared this chemical knowledge with Watson and Crick when she pointed out to them that their first model (from 1951, with the phosphates inside) was obviously wrong.

Crick described what he saw as the failure of Maurice Wilkins and Rosalind Franklin to cooperate and work towards finding a molecular model of DNA as a major reason why he and Watson eventually made a second attempt to do so. They asked for, and received, permission to do so from both William Lawrence Bragg and Wilkins. In order to construct their model of DNA, Watson and Crick made use of information from unpublished X-ray diffraction images of Franklin's (shown at meetings and freely shared by Wilkins), including preliminary accounts of Franklin's results/photographs of the X-ray images that were included in a written progress report for the King's College laboratory of Sir John Randall from late 1952.

It is a matter of debate whether Watson and Crick should have had access to Franklin's results without her knowledge or permission, and before she had a chance to formally publish the results of her detailed analysis of her X-ray diffraction data which were included in the progress report. However, Watson and Crick found fault in her steadfast assertion that, according to her data, a helical structure was not the only possible shape for DNA—so they had a dilemma. In an effort to clarify this issue, Max Ferdinand Perutz later published what had been in the progress report,<sup>[31]</sup> and suggested that nothing was in the report that Franklin herself had not said in her talk (attended by Watson) in late 1951. Further, Perutz explained that the report was to a Medical Research Council (MRC) committee that had been created in order to "establish contact between the different groups of people working for the Council". Randall's and Perutz's laboratories were both funded by the MRC.

It is also not clear how important Franklin's unpublished results from the progress report actually were for the model-building done by Watson and Crick. After the first crude X-ray diffraction images of DNA were collected in the 1930s, William Astbury had talked about stacks of nucleotides spaced at 3.4 angström (0.34 nanometre) intervals in DNA. A citation to Astbury's earlier X-ray diffraction work was one of only eight references in Franklin's first paper on DNA.<sup>[32]</sup> Analysis of Astbury's published DNA results and the better X-ray diffraction images collected by Wilkins and Franklin revealed the helical nature of DNA. It was possible to predict the number of bases stacked within a single turn of the DNA helix (10 per turn; a full turn of the helix is 27 angströms [2.7 nm] in the compact A form, 34 angströms [3.4 nm] in the wetter B form). Wilkins shared this information about the B form of DNA with Crick and Watson. Crick did not see Franklin's B form X-ray images (Photo 51) until after the DNA double helix model was published.<sup>[33]</sup>

One of the few references cited by Watson and Crick when they published their model of DNA, was to a published article that included Sven Furberg's DNA model that had the bases on the inside. Thus, the Watson and Crick model was not the first "bases in" model to be published. Furberg's results had also provided the correct orientation of the DNA sugars with respect to the bases. During their model building, Crick and Watson learned that an anti-parallel orientation of the two nucleotide chain backbones worked best to orient the base pairs in the centre of a double helix. Crick's access to Franklin's progress report of late 1952 is what made Crick confident that DNA was a double helix

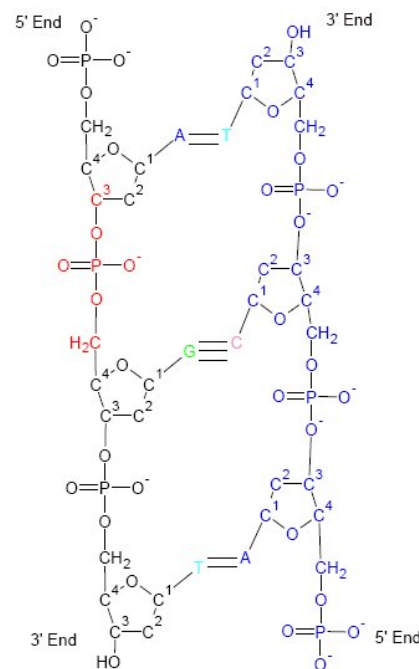
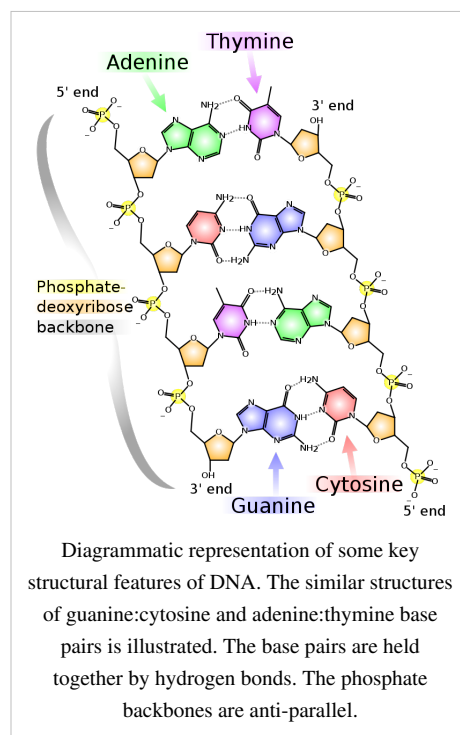


Diagram that emphasizes the phosphate backbone of DNA. Watson and Crick first made helical models with the phosphates at the center of the helices.

with anti-parallel chains, but there were other chains of reasoning and sources of information that also led to these conclusions.<sup>[34]</sup>

As a result of leaving King's College for another institution, Franklin was asked by John Randall to give up her work on DNA. When it became clear to Wilkins and the supervisors of Watson and Crick that Franklin was going to the new job, and that Linus Pauling was working on the structure of DNA, they were willing to share Franklin's data with Watson and Crick, in the hope that they could find a good model of DNA before Pauling was able. Franklin's X-ray diffraction data for DNA and her systematic analysis of DNA's structural features was useful to Watson and Crick in guiding them towards a correct molecular model. The key problem for Watson and Crick, which could not be resolved by the data from King's College, was to guess how the nucleotide bases pack into the core of the DNA double helix.

Another key to finding the correct structure of DNA was the so-called Chargaff ratios, experimentally determined ratios of the nucleotide subunits of DNA: the amount of guanine is equal to cytosine and the amount of adenine is equal to thymine. A visit by Erwin Chargaff to England in 1952 reinforced the salience of this important fact for Watson and Crick. The significance of these ratios for the structure of DNA were not recognized until Watson, persisting in building structural models, realized that A:T and C:G pairs are structurally similar. In particular, the length of each base pair is the same. The base pairs are held together by hydrogen bonds, the same non-covalent interaction that stabilizes the protein  $\alpha$ -helix. Watson's recognition of the A:T and C:G pairs was aided by information from Jerry Donohue about the most likely structures of the nucleobases.<sup>[35]</sup> After the discovery of the hydrogen bonded A:T and C:G pairs, Watson and Crick soon had their double helix model of DNA with the hydrogen bonds at the core of the helix providing a way to "unzip" the two complementary strands for easy replication: the last key requirement for a likely model of the genetic molecule. As important as Crick's contributions to the discovery of the double helical DNA model were, he stated that without the chance to collaborate with Watson, he would not have found the structure by himself.<sup>[36]</sup>



Crick did tentatively attempt to perform some experiments on nucleotide base pairing, but he was more of a theoretical than an experimental biologist. There was another near-discovery of the base pairing rules in early 1952. Crick had started to think about interactions between the bases. He asked John Griffith to try to calculate attractive interactions between the DNA bases from chemical principles and quantum mechanics. Griffith's best guess was that A:T and G:C were attractive pairs. At that time, Crick was not aware of Chargaff's rules and he made little of Griffith's calculations, although it did start him thinking about complementary replication. Identification of the correct base-pairing rules (A-T, G-C) was achieved by Watson "playing" with cardboard cut-out models of the nucleotide bases, much in the manner that Linus Pauling had discovered the protein alpha helix a few years earlier. The Watson and Crick discovery of the DNA double helix structure was made possible by their willingness to combine theory, modeling and experimental results (albeit mostly done by others) to achieve their goal.

The discovery was made on February 28, 1953; the first Watson/Crick paper appeared in *Nature* on April 25, 1953. Sir Lawrence Bragg, the director of the Cavendish Laboratory, where Watson and Crick worked, gave a talk at Guys Hospital Medical School in London on Thursday, May 14, 1953 which resulted in an article by Ritchie Calder in *The News Chronicle* of London, on Friday, May 15, 1953, entitled "Why You Are You. Nearer Secret of Life." The news reached readers of *The New York Times* the next day; Victor K. McElheny, in researching his biography, "Watson and DNA: Making a Scientific Revolution", found a clipping of a six-paragraph *New York Times* article written



from London and dated May 16, 1953 with the headline "Form of 'Life Unit' in Cell Is Scanned." The article ran in an early edition and was then pulled to make space for news deemed more important. (The New York Times subsequently ran a longer article on June 12, 1953). The Cambridge University undergraduate newspaper *Varsity* also ran its own short article on the discovery on Saturday, May 30, 1953. Bragg's original announcement of the discovery at a Solvay conference on proteins in Belgium on 8 April 1953 went unreported by the British press!

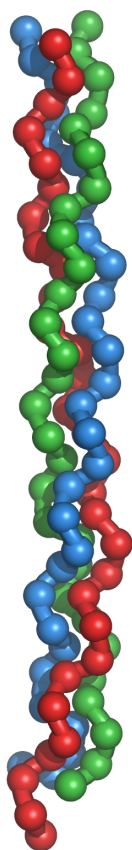
## Molecular biology

In 1954, at the age of 37, Crick completed his Ph.D. thesis: "X-Ray Diffraction: Polypeptides and Proteins" and received his degree. Crick then worked in the laboratory of David Harker at Brooklyn Polytechnic Institute, where he continued to develop his skills in the analysis of X-ray diffraction data for proteins, working primarily on ribonuclease and the mechanisms of protein synthesis. David Harker, the American X-ray crystallographer, was described as "the John Wayne of crystallography" by Vittorio Luzzati, a crystallographer at the Centre for Molecular Genetics in Gif-sur-Yvette near Paris, who had worked with Rosalind Franklin.

After the discovery of the double helix model of DNA, Crick's interests quickly turned to the biological implications of the structure. In 1953, Watson and Crick published another article in *Nature* which stated: "it therefore seems likely that the precise sequence of the bases is the code that carries the genetical information".<sup>[38]</sup>



Crick and Watson DNA model built in 1953, was reconstructed<sup>[37]</sup> largely from its original pieces in 1973 and donated to the National Science Museum in London.



Collagen triple helix.

In 1956, Crick and Watson speculated on the structure of small viruses. They suggested that spherical viruses such as Tomato bushy stunt virus had icosahedral symmetry and were made from 60 identical subunits.<sup>[39]</sup>

After his short time in New York, Crick returned to Cambridge where he worked until 1976, at which time he moved to California. Crick engaged in several X-ray diffraction collaborations such as one with Alexander Rich on the structure of collagen.<sup>[40]</sup> However, Crick was quickly drifting away from continued work related to his expertise in the interpretation of X-ray diffraction patterns of proteins.

George Gamow established a group of scientists interested in the role of RNA as an intermediary between DNA as the genetic storage molecule in the nucleus of cells and the synthesis of proteins in the cytoplasm. It was clear to Crick that there had to be a code by which a short sequence of nucleotides would specify a particular amino acid in a newly synthesized protein. In 1956, Crick wrote an informal paper about the genetic coding problem for the small group of scientists in Gamow's RNA group.<sup>[41]</sup> In this article, Crick reviewed the evidence supporting the idea that there was a common set of about 20 amino acids used to synthesize proteins. Crick proposed that there was a corresponding set of small "adaptor molecules" that would hydrogen bond to short sequences of a nucleic acid, and also link to one of the amino acids. He also explored the many theoretical possibilities by which short nucleic acid sequences might code for the 20 amino acids.

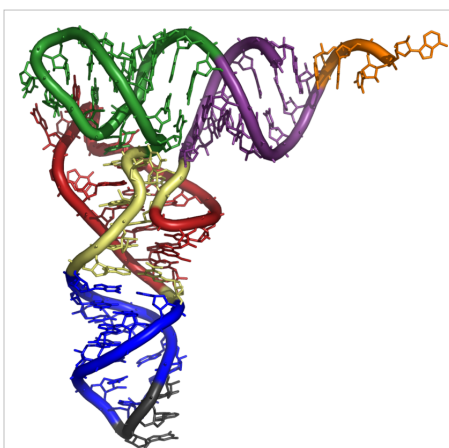
During the mid-to-late 1950s Crick was very much intellectually engaged in sorting out the mystery of how proteins are synthesized. By 1958, Crick's thinking had matured and he could list in an orderly way all of the key features of the protein synthesis process:<sup>[42]</sup>

- genetic information stored in the sequence of DNA molecules
- a "messenger" RNA molecule to carry the instructions for making one protein to the cytoplasm
- adaptor molecules ("they might contain nucleotides") to match short sequences of nucleotides in the RNA messenger molecules to specific amino acids
- ribonucleic-protein complexes that catalyse the assembly of amino acids into proteins according to the messenger RNA

The adaptor molecules were eventually shown to be tRNAs and the catalytic "ribonucleic-protein complexes" became known as ribosomes.

An important step was later realization (in 1960) that the messenger

RNA was not the same as the ribosomal RNA. None of this, however, answered the fundamental theoretical question of the exact nature of the genetic code. In his 1958 article, Crick speculated, as had others, that a triplet of nucleotides could code for an amino acid. Such a code might be "degenerate", with  $4 \times 4 \times 4 = 64$  possible triplets of the four nucleotide subunits while there were only 20 amino acids. Some amino acids might have multiple triplet codes.



Molecular model of a tRNA molecule. Crick predicted that such adaptor molecules might exist as the links between codons and amino acids.

Crick also explored other codes in which, for various reasons, only some of the triplets were used, "magically" producing just the 20 needed combinations. Experimental results were needed; theory alone could not decide the nature of the code. Crick also used the term "central dogma" to summarize an idea that implies that genetic information flow between macromolecules would be essentially one-way:

**DNA → RNA → Protein**

Some critics thought that by using the word "dogma", Crick was implying that this was a rule that could not be questioned, but all he really meant was that it was a compelling idea without much solid evidence to support it. In his thinking about the biological processes linking DNA genes to proteins, Crick made explicit the distinction between the materials involved, the energy required, and the information flow. Crick was focused on this third component (information) and it became the organizing principle of what became known as molecular biology. Crick had by this time become a highly influential theoretical molecular biologist.

Proof that the genetic code is a degenerate triplet code finally came from genetics experiments, some of which were performed by Crick.<sup>[43]</sup> The details of the code came mostly from work by Marshall Nirenberg and others who synthesized synthetic RNA molecules and used them as templates for *in vitro* protein synthesis.<sup>[44]</sup>

## **Controversy about using King's College London's results**

An enduring controversy has been generated by Watson and Crick's use of DNA X-ray diffraction data collected by Rosalind Franklin and her student Raymond Gosling. The controversy arose from the fact that some of the data were shown to them, without her knowledge, by Maurice Wilkins and Max Perutz.<sup>[45]</sup> Her experimental results provided estimates of the water content of DNA crystals, and these results were most consistent with the three sugar-phosphate backbones being on the outside of the molecule.<sup>[46]</sup> Franklin personally told Crick and Watson that the backbones had to be on the outside, whilst vehemently stating that her data did not force one to conclude that DNA has a helical structure. Her identification of the space group for DNA crystals revealed to Crick that the DNA strands were antiparallel, which helped Watson and Crick decide to look for DNA models with two antiparallel polynucleotide strands. The X-ray diffraction images collected by Franklin provided the best evidence for the helical nature of DNA—but she failed to recognise this fact. However Franklin's experimental work proved important in Crick and Watson's development of the correct model.

Prior to publication of the double helix structure, Watson and Crick had little interaction with Franklin. Crick and Watson felt that they had benefited from collaborating with Maurice Wilkins. They offered him a co-authorship on the article that first described the double helix structure of DNA. Wilkins turned down the offer, and was in part responsible for the terse character of the acknowledgment of experimental work done at King's College London. Rather than make any of the DNA researchers at King's College co-authors on the Watson and Crick double helix article, the solution was to publish two additional papers from King's College along with the helix paper. Brenda Maddox suggested that because of the importance of her experimental results in Watson and Crick's model building and theoretical analysis, Franklin should have had her name on the original Watson and Crick paper in *Nature*.<sup>[47]</sup> Franklin and Gosling submitted their own joint 'second' paper to *Nature* at the same time as Wilkins, Stokes, and Wilson submitted theirs (i.e. the 'third' paper on DNA).

## Views on religion

Crick once joked, "Christianity may be OK between consenting adults in private but should not be taught to young children."<sup>[48]</sup>

In his book *Of Molecules and Men*, Crick expressed his views on the relationship between science and religion.<sup>[49]</sup> After suggesting that it would become possible for people to wonder if a computer might be programmed so as to have a soul, he wondered: at what point during biological evolution did the first organism have a soul? At what moment does a baby get a soul? Crick stated his view that the idea of a non-material soul that could enter a body and then persist after death is just that, an imagined idea. For Crick, the mind is a product of physical brain activity and the brain had evolved by natural means over millions of years. Crick felt that it was important that evolution by natural selection be taught in public schools and that it was regrettable that English schools had compulsory religious instruction. Crick felt that a new scientific world view was rapidly being established, and predicted that once the detailed workings of the brain were eventually revealed, erroneous Christian concepts about the nature of humans and the world would no longer be tenable; traditional conceptions of the "soul" would be replaced by a new understanding of the physical basis of mind. He was sceptical of organized religion, referring to himself as a sceptic and an agnostic with "a strong inclination towards atheism".<sup>[50]</sup>

In 1960, Crick accepted a fellowship at Churchill College Cambridge, one factor being that the new college did not have a chapel. Sometime later a large donation was made to establish a chapel and the fellowship elected to accept it. Crick resigned his fellowship in protest.<sup>[51]</sup>

In October 1969, Crick participated in a celebration of the 100th year of the journal *Nature*. Crick attempted to make some predictions about what the next 30 years would hold for molecular biology. His speculations were later published in *Nature*.<sup>[52]</sup> Near the end of the article, Crick briefly mentioned the search for life on other planets, but he held little hope that extraterrestrial life would be found by the year 2000. He also discussed what he described as a possible new direction for research, what he called "biochemical theology". Crick wrote, "So many people pray that one finds it hard to believe that they do not get some satisfaction from it".

Crick suggested that it might be possible to find chemical changes in the brain that were molecular correlates of the act of prayer. He speculated that there might be a detectable change in the level of some neurotransmitter or neurohormone when people pray. Crick may have been imagining substances such as dopamine that are released by the brain under certain conditions and produce rewarding sensations. Crick's suggestion that there might someday be a new science of "biochemical theology" seems to have been realized under an alternative name: there is now the new field of neurotheology.<sup>[53]</sup> Crick's view of the relationship between science and religion continued to play a role in his work as he made the transition from molecular biology research into theoretical neuroscience.

In a book entitled *Life Itself: Its Origin and Nature* (page 88), Crick wrote: "An honest man, armed with all the knowledge available to us now, could only state that in some sense, the origin of life appears at the moment to be almost a miracle, so many are the conditions which would have had to have been satisfied to get it going."

## Directed panspermia

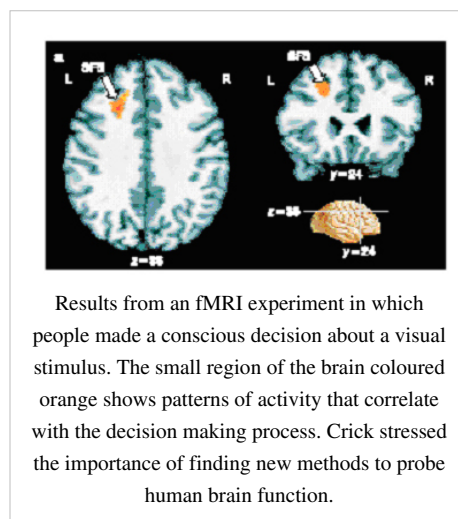
During the 1960s, Crick became concerned with the origins of the genetic code. In 1966, Crick took the place of Leslie Orgel at a meeting where Orgel was to talk about the origin of life. Crick speculated about possible stages by which an initially simple code with a few amino acid types might have evolved into the more complex code used by existing organisms.<sup>[54]</sup> At that time, everyone thought of proteins as the only kind of enzymes and ribozymes had not yet been found. Many molecular biologists were puzzled by the problem of the origin of a protein replicating system that is as complex as that which exists in organisms currently inhabiting Earth. In the early 1970s, Crick and Orgel further speculated about the possibility that the production of living systems from molecules may have been a very rare event in the universe, but once it had developed it could be spread by intelligent life forms using space travel technology, a process they called "Directed Panspermia".<sup>[55]</sup> In a retrospective article,<sup>[56]</sup> Crick and Orgel noted that

they had been overly pessimistic about the chances of abiogenesis on Earth when they had assumed that some kind of self-replicating protein system was the molecular origin of life.

Crick addressed the Origin of Protein Synthesis in a paper with Sydney Brenner, Aaron Klug.<sup>[57]</sup> In this paper, they speculate that code constraints on nucleotide sequences allow protein synthesis without the need for a ribosome. It, however, requires a five base binding between the mRNA and tRNA with a flip of the anti-codon creating a triplet coding, even though it is a five base physical interaction. Thomas H. Jukes pointed out that the code constraints on the mRNA sequence required for this translation mechanism is still preserved.

## Neuroscience, other interests

Crick's period at Cambridge was the pinnacle of his long scientific career, but he left Cambridge in 1977 after 30 years, having been offered (and having refused) the Mastership of Gonville & Caius. James Watson claimed at a Cambridge conference marking the 50th anniversary of the discovery of the structure of DNA in 2003: "Now perhaps it's a pretty well kept secret that one of the most uninspiring acts of Cambridge University over this past century was to turn down Francis Crick when he applied to be the Professor of Genetics, in 1958. Now there may have been a series of arguments, which lead them to reject Francis. It was really saying, don't push us to the frontier." The apparently "pretty well kept secret" had already been recorded in Soraya De Chadarevian's "Designs For Life: Molecular Biology After World War II", published by CUP in 2002. His major contribution to molecular biology in Cambridge is well documented in *The History of the University of Cambridge: Volume 4 (1870 to 1990)*, which was published by Cambridge University Press in 1992.



According to the University of Cambridge's genetics department official website <sup>[58]</sup>, the electors of the professorship could not reach consensus, prompting the intervention of then University Vice-Chancellor Lord Adrian. Lord Adrian first offered the professorship to a compromise candidate, Guido Pontecorvo, who refused, and is said to have offered it then to Crick, who also refused.

In 1976, Crick took a sabbatical year at the Salk Institute for Biological Studies in La Jolla, California. Crick had been a nonresident fellow of the Institute since 1960. Crick wrote, "I felt at home in Southern California."<sup>[59]</sup> After the sabbatical, Crick left Cambridge in order to continue working at the Salk Institute. He was also a professor at the University of California, San Diego. He taught himself neuroanatomy and studied many other areas of neuroscience research. It took him several years to disengage from molecular biology because exciting discoveries continued to be made, including the discovery of alternative splicing and the discovery of restriction enzymes, which helped make possible genetic engineering. Eventually, in the 1980s, Crick was able to devote his full attention to his other interest, consciousness. His autobiographical book, *What Mad Pursuit*, includes a description of why he left molecular biology and switched to neuroscience.

Upon taking up work in theoretical neuroscience, Crick was struck by several things:

- there were many isolated subdisciplines within neuroscience with little contact between them
- many people who were interested in behaviour treated the brain as a black box
- consciousness was viewed as a taboo subject by many neurobiologists

Crick hoped he might aid progress in neuroscience by promoting constructive interactions between specialists from the many different subdisciplines concerned with consciousness. He even collaborated with neurophilosophers such as Patricia Churchland. In 1983, as a result of their studies of computer models of neural networks, Crick and

Mitchison proposed that the function of REM sleep is to remove certain modes of interactions in networks of cells in the mammalian cerebral cortex; they called this hypothetical process 'reverse learning' or 'unlearning'. In the final phase of his career, Crick established a collaboration with Christof Koch that led to publication of a series of articles on consciousness during the period spanning from 1990<sup>[60]</sup> to 2005. Crick made the strategic decision to focus his theoretical investigation of consciousness on how the brain generates visual awareness within a few hundred milliseconds of viewing a scene. Crick and Koch proposed that consciousness seems so mysterious because it involves very short-term memory processes that are as yet poorly understood. Crick also published a book describing how neurobiology had reached a mature enough stage so that consciousness could be the subject of a unified effort to study it at the molecular, cellular and behavioural levels.<sup>[61]</sup> Crick's book *The Astonishing Hypothesis* made the argument that neuroscience now had the tools required to begin a scientific study of how brains produce conscious experiences. Crick was skeptical about the value of computational models of mental function that are not based on details about brain structure and function.

## Reactions to Crick and his work

Crick has widely been described as talkative, brash, and lacking modesty.<sup>[62]</sup> His personality combined with his scientific accomplishments produced many opportunities for Crick to stimulate reactions from others, both inside and outside of the scientific world, which was the centre of his intellectual and professional life.<sup>[63]</sup> Crick spoke rapidly, and rather loudly, and had an infectious and reverberating laugh, and a lively sense of humour. One colleague from the Salk Institute described him as "a brainstorming intellectual powerhouse with a mischievous smile.... Francis was never mean-spirited, just incisive. He detected microscopic flaws in logic. In a room full of smart scientists, Francis continually reearned his position as the heavyweight champ."<sup>[64]</sup>

## Eugenics

Crick occasionally expressed his views on eugenics, usually in private letters. For example, Crick advocated a form of positive eugenics in which wealthy parents would be encouraged to have more children.<sup>[65]</sup> He once remarked, "In the long run, it is unavoidable that society will begin to worry about the character of the next generation... It is not a subject at the moment which we can tackle easily because people have so many religious beliefs and until we have a more uniform view of ourselves I think it would be risky to try and do anything in the way of eugenics... I would be astonished if, in the next 100 or 200 years, society did not come round to the view that they would have to try to improve the next generation in some extent or one way or another."

## Creationism

It has been suggested by some observers that Crick's speculation about panspermia "fits neatly into the intelligent design concept."<sup>[66]</sup> Crick's name was raised in this context in the *Kitzmiller v. Dover Area School District* trial over the teaching of intelligent design. Crick was, however, a firm critic of Young earth creationism. In the 1987 United States Supreme Court case *Edwards v. Aguillard*, Crick joined a group of other Nobel laureates who advised that, "'Creation-science' simply has no place in the public-school science classroom."<sup>[67]</sup> Crick was also an advocate for the establishment of Darwin Day as a British national holiday.<sup>[68]</sup>



## Recognition

In addition to his third share of the 1962 Nobel prize for Physiology or Medicine, he received many awards and honours, including the Royal and Copley medals of the Royal Society (1972 and 1975), and also the Order of Merit (on November 27, 1991); he refused an offer of a CBE in 1963 and later refused an offer of a knighthood, but was often referred to in error as 'Sir Francis Crick' and even on occasions as 'Lord Crick'; Richard Lewontin's review of *The Double Helix* by James Watson in "The Chicago Sunday Times" on February 25, 1968 contained an astonishing four references to "Sir Francis Crick" - in error. This mistake is being repeated to the present day.

On Saturday, October 20, 1962 the award of Nobel prizes to John Kendrew and Max Perutz, and to Crick, Watson, and Wilkins was satirised in a short sketch in the BBC TV programme *That Was The Week That Was* with the Nobel Prizes being referred to as 'The Alfred Nobel Peace Pools.'

### The Francis Crick Prize Lectures at The Royal Society, London

The Francis Crick Lecture was established in 2003 following an endowment by his former colleague, Sydney Brenner, joint winner of the 2002 Nobel Prize in Physiology and Medicine.<sup>[69]</sup> The lecture is delivered annually in any field of biological sciences, with preference given to the areas in which Francis Crick himself worked. Importantly, the lectureship is aimed at younger scientists, ideally under 40, or whose career progression corresponds to this age.

### The Francis Crick Graduate Lectures at the University of Cambridge

The University of Cambridge Graduate School of Biological, Medical and Veterinary Sciences hosts The Francis Crick Graduate Lectures. The first two lectures were by John Gurdon and Tim Hunt.<sup>[70] [71]</sup>

"For my generation, Francis Crick was probably the most obviously influential presence. He was often at lunch in the canteen of the Laboratory of Molecular Biology where he liked to explain what he was thinking about, and he was always careful to make sure that everyone round the table really understood. He was a frequent presence at talks in and around Cambridge, where he liked to ask questions. Sometimes, I remember thinking, they seemed slightly ignorant questions to which a man of his extraordinary range and ability ought to have known the answers. Only slowly did it dawn on me that he only and always asked questions when he was unclear or unsure, a great lesson." (Tim Hunt, first Francis Crick Graduate Lecturer: June 2005)

The wording on the new DNA sculpture (which was donated by James Watson) outside Clare College's Thirkill Court, Cambridge, England is

a) on the base:

- i) "These strands unravel during cell reproduction. Genes are encoded in the sequence of bases."
- ii) "The double helix model was supported by the work of Rosalind Franklin and Maurice Wilkins."

b) on the helices:

- i) "The structure of DNA was discovered in 1953 by Francis Crick and James Watson while Watson lived here at Clare."
- ii) "The molecule of DNA has two helical strands that are linked by base pairs Adenine - Thymine or Guanine - Cytosine."



Stained glass window in the dining hall of Caius College, in Cambridge, commemorating Francis Crick and representing the structure of DNA.

The aluminium sculpture stands fifteen feet high. It took a pair of technicians a fortnight to build it. For the artist responsible it was an opportunity to create a monument that brings together the themes of science and nature; Charles Jencks, Sculptor said "It embraces the trees, you can sit on it and the ground grows up and it twists out of the ground. So it's truly interacting with living things like the turf, and that idea was behind it and I think it does celebrate life and DNA." Tony Badger, Master of Clare, said: "It is wonderful to have this lasting reminder of his achievements while he\* was at Clare and the enormous contribution he\* and Francis Crick have made to our understanding of life on earth." \* James D. Watson.

[72] Westminster City Council unveiled a green plaque to Francis Crick on the front façade of 56 St George's Square, Pimlico, London SW1 on the 20 June 2007; Crick lived in the first floor flat, together with Robert Dougall of BBC radio and later TV fame, a former Royal Navy associate.; Robert Dougall had replaced Georg Kreisel who left the flat in 1946.

Crick was elected a fellow of CSICOP in 1983 and a Humanist Laureate of the International Academy of Humanism in the same year. In 1995, Francis Crick was one of the original endorsers of the Ashley Montagu Resolution to petition for an end to the genital mutilation of children.

Another sculpture entitled *Discovery*, was installed on Tuesday, 13 December 2005 and a formal ribbon-cutting ceremony was held on Thursday, 15 December 2005 at 11.00am in Abington Street, Northampton. According to the late Mr Lynn Wilson, chairman of the Wilson Foundation, "The sculpture celebrates the life of a world class scientist who must surely be considered the greatest Northamptonian of all time - by discovering DNA he unlocked the whole future of genetics and the alphabet of life."

- Fellow of the Royal Society
- Fellow International Academy of Humanism
- Fellow CSICOP

## Books by Francis Crick

- *Of Molecules and Men* (Prometheus Books, 2004; original edition 1967) ISBN 1-59102-185-5
- *Life Itself* (Simon & Schuster, 1981) ISBN 0-671-25562-2
- *What Mad Pursuit: A Personal View of Scientific Discovery* (Basic Books reprint edition, 1990) ISBN 0-465-09138-5
- *The Astonishing Hypothesis: The Scientific Search For The Soul* (Scribner reprint edition, 1995) ISBN 0-684-80158-2
- Kreiseliana: about and around Georg Kreisel; ISBN 1-56881-061-X; 495 pages. For pages 25 – 32 "Georg Kreisel: a Few Personal Recollections" contributed by Francis Crick.

## Books about Francis Crick and the structure of DNA discovery

- John Bankston, Francis Crick and James D. Watson; *Francis Crick and James Watson: Pioneers in DNA Research* (Mitchell Lane Publishers, Inc., 2002) ISBN 1-58415-122-6
- Soraya De Chadarevian; *Designs For Life: Molecular Biology After World War II*, CUP 2002, 444 pp; ISBN 0-521-57078-6
- Edwin Chargaff; *Heraclitean Fire*, Rockefeller Press, 1978
- S. Chomet (Ed.), "*D.N.A. Genesis of a Discovery*", 1994, Newman- Hemisphere Press, London
- Dickerson, Richard E.; "*Present at the Flood: How Structural Molecular Biology Came About*", Sinauer, 2005; ISBN 0-878-93168-6;
- Edward Edelson, "*Francis Crick And James Watson: And the Building Blocks of Life*" Oxford University Press, 2000, ISBN 0-19-513971-2.



- John Finch; 'A Nobel Fellow On Every Floor', Medical Research Council 2008, 381 pp, ISBN 978-1840469-40-0; this book is all about the MRC Laboratory of Molecular Biology, Cambridge.
- Hager, Thomas; "*Force of Nature: The Life of Linus Pauling*", Simon & Schuster 1995; ISBN 0-684-80909-5
- Graeme Hunter; *Light Is A Messenger, the life and science of William Lawrence Bragg*, ISBN 0-19-852921-X; Oxford University Press, 2004.
- Horace Freeland Judson, "*The Eighth Day of Creation. Makers of the Revolution in Biology*"; Penguin Books 1995, first published by Jonathan Cape, 1977; ISBN 0-14-017800-7.
- Torsten Krude (Ed.); *DNA Changing Science and Society* (ISBN 0-521-82378-1) CUP 2003. (The Darwin Lectures for 2003, including one by Sir Aaron Klug on Rosalind Franklin's involvement in the determination of the structure of DNA).
- Brenda Maddox *Rosalind Franklin: The Dark Lady of DNA*, 2002. ISBN 0-00-655211-0.
- Robert Olby; *The Path to The Double Helix: Discovery of DNA*; first published in October 1974 by MacMillan, with foreword by Francis Crick; ISBN 0-486-68117-3; revised in 1994, with a 9-page postscript.
- Robert Olby; Oxford National Dictionary article: 'Crick, Francis Harry Compton (1916–2004)', Oxford Dictionary of National Biography, Oxford University Press, January 2008;
- Robert Olby; "Francis Crick: Hunter of Life's Secrets", Cold Spring Harbor Laboratory Press, ISBN 978-087969798-3, published on 25 August 2009. [73]
- Matt Ridley; *Francis Crick: Discoverer of the Genetic Code (Eminent Lives)* first published in June 2006 in the USA and then in the UK September 2006, by HarperCollins Publishers; 192 pp, ISBN 0-06-082333-X.
- Anne Sayre. 1975. *Rosalind Franklin and DNA*. New York: W.W. Norton and Company. ISBN 0-393-32044-8.
- James D. Watson; *The Double Helix: A Personal Account of the Discovery of the Structure of DNA*, Atheneum, 1980, ISBN 0-689-70602-2 (first published in 1968) is a very readable firsthand account of the research by Crick and Watson. The book also formed the basis of the award winning television dramatization *Life Story* by BBC Horizon (also broadcast as *Race for the Double Helix*).
- James D. Watson; *The Double Helix: A Personal Account of the Discovery of the Structure of DNA*; The Norton Critical Edition, which was published in 1980, edited by Gunther S. Stent: ISBN 0-393-01245-X. (It does not include Erwin Chargaff's critical review unfortunately.)
- James D. Watson; "Avoid boring people and other lessons from a life in science" New York: Random House. ISBN 978-0-375-41284-4, 366pp
- Maurice Wilkins; *The Third Man of the Double Helix: The Autobiography of Maurice Wilkins* ISBN 0-19-860665-6.

## See also

- Neural correlates of consciousness
- Molecular structure of Nucleic Acids
- Crick's wobble hypothesis
- Crick, Brenner et al. experiment
- Reverse learning

## External links

### Crick papers

- [74] Crick's personal papers at Mandeville Special Collections Library, Geisel Library, University of California, San Diego
- Francis Crick Archive - Papers by Francis Crick are available for study at the Wellcome Library's Archives and Manuscripts department. These papers include those dealing with Crick's career after he moved to the Salk Institute in San Diego. The Crick papers <sup>[75]</sup>
- Comprehensive list of pdf files of Crick's papers from 1950 to 1990 <sup>[76]</sup> - National Library of Medicine.
- Francis Crick papers <sup>[77]</sup> - *Nature.com*
- <http://www.intuition.org/txt/crick2.htm> for Crick's comments on LSD
- Manuscripts and Correspondence - Mark Bretscher <sup>[78]</sup> Discovery of Crick's original scientific material in Cambridge, England.
- Key Participants: Francis H. C. Crick <sup>[79]</sup> - *Linus Pauling and the Race for DNA: A Documentary History*

### Hear or see Crick

- An interview with Francis Crick and Christof Koch, 2001 <sup>[80]</sup>
- Listen to Francis Crick <sup>[81]</sup>
- Presentation speech <sup>[82]</sup> at the Nobel Prize ceremony in 1962.
- [83] web of stories video
- *The Quest for Consciousness* <sup>[84]</sup> - *The Quest for Consciousness* - 65 minute audio program - a conversation on Consciousness with neurobiologist Francis Crick of the Salk Institute and neurobiologist Christof Koch from Caltech.
- Listen <sup>[85]</sup> to Francis Crick and James Watson talking on the BBC in 1962, 1972, and 1974.
- The Impact of Linus Pauling on Molecular Biology <sup>[86]</sup> - a 1995 talk delivered by Crick at Oregon State University

### About his work

- [75] The Crick Papers at the Wellcome Trust.
- "Quiet debut for the double helix" <sup>[87]</sup> by Professor Robert Olby, *Nature* **421** (23 January 2003): 402-405.
- Reading list <sup>[88]</sup> for discovery of DNA story from the National Centre for Biotechnology Education.

### About his life

- Salk Institute Press Release <sup>[89]</sup> on the death of Francis Crick.
  - BBC News: Francis Crick dies aged 88 <sup>[90]</sup>
  - Francis Crick <sup>[91]</sup> (Archived <sup>[92]</sup> 2009-10-31) - MSN Encarta
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## Miscellaneous

- National DNA Day, 25 April 2006 Moderated Chat Transcript Archive <sup>[93]</sup>
- Obituary <sup>[94]</sup> in "The Times" (London) of Francis Crick, 30 July 2004.
- Independent On Line article <sup>[95]</sup> about Consciousness, 7 June 2006.
- Francis Crick Obituary <sup>[96]</sup> *The Biochemist*
- Obituary: Francis H. C. Crick (1916-2004) <sup>[97]</sup> by David M. Eagleman, in *Vision Research*
- Obituary: Francis Crick's Legacy for Neuroscience <sup>[98]</sup> by Ralph M. Siegel and Edward M. Callaway, in *PLoS Biology*
- 100 Scientists and Thinkers: James Watson and Francis Crick <sup>[99]</sup> from TIME magazine.
- Francis Crick: Nobel Prize 1962, Physiology or Medicine <sup>[100]</sup>
- Associated Press story on the death of Francis Crick <sup>[101]</sup>
- First press stories on DNA <sup>[13]</sup> but for the 'second' DNA story in *The New York Times*, see: <http://www.nytimes.com/packages/pdf/science/dna-article.pdf> - for reproduction of the original text in June 1953.
- 'Death' of DNA Helix (Crystalline) joke funeral card.
- Lynne Elkins' article on Franklin <sup>[102]</sup>.
- 50th anniversary series of articles <sup>[103]</sup> -from *The New York Times*.
- Quotes <sup>[104]</sup> of Robert Olby on exactly who *may* have discovered the structure of DNA.
- listen to Matt Ridley <sup>[105]</sup> talking about Francis Crick.
- [106] A celebration of Francis Crick's life in science.
- The People's Archive interview [107]
- [108] Odile Crick's page (with music!) on the Crick family web site.
- [109] Obituary by Peter Lawrence and Mark Bretscher, "Current Biology".
- [110] Article by Mark Steyn from The Atlantic in 2004.
- [111] Review of "Francis Crick: Hunter of Life's Secrets" in 'Current Biology'.

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- [5] Crick, Francis (1990). *What Mad Pursuit: a Personal View of Scientific Discovery*. Basic Books reprint edition. pp. 145. ISBN 0-465-09138-5. — Crick described himself as **agnostic, with a "strong inclination towards atheism"**.
- [6] Chapters 1 and 2 of *What Mad Pursuit* by Francis Crick — provide Crick's description of his early life and education
- [7] Page 13 of *What Mad Pursuit* by Francis Crick.
- [8] *Nature*, Obituary, volume 430, 19 August 2004, p 845
- [9] Bio at Wellcome Trust ([http://genome.wellcome.ac.uk/doc\\_wtd021051.html](http://genome.wellcome.ac.uk/doc_wtd021051.html))
- [10] "Francis Crick, Co-Discoverer of DNA, Dies at 88" (<http://query.nytimes.com/gst/fullpage.html?sec=health&res=9E06E7D7113DF933A05754C0A9629C8B63>). *The New York Times*. 30 July 2004. . Retrieved 2007-07-21. "Francis H. C. Crick, co-discoverer of the structure of DNA, the genetic blueprint for life, and the leading molecular biologist of his age, died on Wednesday night in a hospital in San Diego. He was 88. He died after a long battle with colon cancer, said Andrew Porterfield, a spokesman for the Salk Institute, where he worked."
- [11] Page 17 of *What Mad Pursuit* by Francis Crick.
- [12] Page 18 of *What Mad Pursuit* by Francis Crick.
- [13] Page 22 of *What Mad Pursuit* by Francis Crick.
- [14] Page 30 of *The Eighth Day of Creation: Makers of the Revolution in Biology* by Horace Freeland Judson published by Cold Spring Harbor Laboratory Press (1996) ISBN 0-87969-478-5.
- [15] Page 25 of *What Mad Pursuit* by Francis Crick.
- [16] Page 32 of *What Mad Pursuit* by Francis Crick.
- [17] Pages 33–34 of *What Mad Pursuit* by Francis Crick.

- [18] Chapter 4 of *What Mad Pursuit* by Francis Crick.
- [19] Page 46 of *What Mad Pursuit* by Francis Crick. "...there was no alternative but to teach X-ray diffraction to myself."
- [20] Atomic Coordinates and Structure Factors for Two Helical Configurations of Polypeptide Chains (<http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=14834145>) by Linus Pauling and Robert B. Corey in *Proc Natl Acad Sci U S A* (1951) volume 37, pages 235–240.
- [21] Page 58 of *What Mad Pursuit* by Francis Crick.
- [22] Cochran W, Crick FHC and Vand V. (1952) "The Structure of Synthetic Polypeptides. I. The Transform of Atoms on a Helix", *Acta Cryst.*, **5**, 581–586.
- [23] See "*Evidence for the Pauling-Corey alpha-Helix in Synthetic Polypeptides*" (1952) *Nature* Volume 169 pages 234–235 (download PDF ([http://profiles.nlm.nih.gov/SC/B/C/D/M/\\_/scbcdm.pdf](http://profiles.nlm.nih.gov/SC/B/C/D/M/_/scbcdm.pdf))). Crick's scientific publications and letters are in the list of Francis Crick's Papers (<http://profiles.nlm.nih.gov/SC/>) from the Wellcome Library or the National Library of Medicine.
- [24] Molecular structure of Nucleic Acids ([http://profiles.nlm.nih.gov/SC/B/B/Y/W/\\_/scbbyw.pdf](http://profiles.nlm.nih.gov/SC/B/B/Y/W/_/scbbyw.pdf)) by James D. Watson and Francis H. C. Crick. *Nature* **171**, 737–738 (1953).
- [25] Francis Crick's 1962 Biography from the Nobel foundation (<http://nobelprize.org/medicine/laureates/1962/crick-bio.html>).
- [26] Crick traced his interest in the physical nature of the gene back to the start of his work in biology, when he was in the Strangeways laboratory; Page 22 of *What Mad Pursuit* by Francis Crick.
- [27] In *The Eighth Day of Creation*, Horace Judson describes the development of Watson's thinking about the physical nature of genes. On page 89, Judson explains that by the time Watson came to Cambridge, he believed genes were made of DNA and he hoped that he could use X-ray diffraction data to determine the structure.
- [28] Page 90, In *The Eighth Day of Creation* by Horace Judson.
- [29] Linus Pauling and the Race for DNA: A Documentary History (<http://osulibrary.oregonstate.edu/specialcollections/coll/pauling/dna/narrative/page13.html>) Special Collections, The Valley Library, Oregon State University.
- [30] Chapter 3 in *The Eighth Day of Creation* by Horace Judson.
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- [34] In chapter 3 of *The Eighth Day of Creation*, Horace Judson describes the development of Watson's and Crick's thinking about the structure of DNA and how it evolved during their model building. Watson and Crick were open to the idea of tentatively ignoring all individual experimental results, in case they might be wrong or misleading. Judson describes how Watson spent a large amount of time *ignoring* Crick's belief (based on Franklin's determination of the space group) that the two backbone strands were antiparallel. On page 176, Judson quotes a letter written by Watson, "The model has been derived almost entirely from stereochemical considerations with the only X-ray consideration being the spacing between the pair of bases 3.4 Å which was originally found by Astbury."
- [35] See Chapter 3 of *The Eighth Day of Creation: Makers of the Revolution in Biology* by Horace Freeland Judson published by Cold Spring Harbor Laboratory Press (1996) ISBN 0-87969-478-5. Judson also lists the publications of W. T. Astbury that described his early X-ray diffraction results for DNA.
- [36] Page 75 of *What Mad Pursuit* by Francis Crick. "If Jim had been killed by a tennis ball, I am reasonably sure I would not have solved the structure alone".
- [37] <http://www.farooqhussain.org/projects/>
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# Maurice Wilkins

| Maurice Wilkins                                                                                      |                                                                   |
|------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| <br>Maurice Wilkins |                                                                   |
| <b>Born</b>                                                                                          | 15 December 1916<br>Pongaroa, Wairarapa,<br>New Zealand           |
| <b>Died</b>                                                                                          | 5 October 2004 (aged 87)<br>Blackheath, London,<br>United Kingdom |
| <b>Nationality</b>                                                                                   | New Zealand                                                       |
| <b>Fields</b>                                                                                        | molecular biologist,                                              |
| <b>Known for</b>                                                                                     | X-ray diffraction, DNA                                            |
| <b>Notable awards</b>                                                                                | Nobel Prize in Physiology or Medicine (1962)                      |

**Maurice Hugh Frederick Wilkins** CBE FRS (15 December 1916 – 5 October 2004) was a New Zealand molecular biologist, and Nobel Laureate who contributed research in the fields of phosphorescence, radar, isotope separation, and X-ray diffraction. He was most widely known for his work at King's College London on the structure of DNA. In recognition of this work, he, Francis Crick and James Watson were awarded the 1962 Nobel Prize for Physiology or Medicine, "for their discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material."<sup>[1]</sup>

## Birth and education



Monument to Maurice Wilkins, Main Street,  
Pongaroa, New Zealand

Wilkins was born in Pongaroa, north Wairarapa, New Zealand where his father, Edgar Henry Wilkins was a medical doctor. His family moved to Birmingham, England when he was 6, where he subsequently attended Wylde Green College and then King Edward's School at the age of 12. He later studied physics at St John's College, Cambridge, then in 1940 he received his Ph.D. in physics at the University of Birmingham with a dissertation on phosphors. During World War II he developed improved radar screens at Birmingham, then worked on isotope separation at the Manhattan Project at the University of California, Berkeley for two years before returning to King's College London. "After the war I wondered what I would do, as I was very disgusted with the dropping of two bombs on civilian centres in Japan," he told Britain's Encounter radio programme in 1999.<sup>[2]</sup>

## Academic career

In 1946 the physicist John Randall was placed in charge of a new biophysics laboratory at King's College. The plan was to hire physicists such as Wilkins to work on problems in biology. When Francis Crick first met Wilkins he was not convinced that the King's College laboratory had anything like a clear plan of attack. There seemed to be a vague hope that by applying techniques like Ultraviolet light microscopy (Wilkins) and electron microscopy (Randall), new insights could be gained into cell structure and function. By 1950, Randall was gearing up the laboratory for work on proteins. His original plan for Rosalind Franklin was that she do X-ray diffraction studies on proteins. Wilkins' work on DNA changed that. By 1951, Randall had established a major effort to solve the structure of collagen and Wilkins and Franklin represented a parallel effort to determine the structure of DNA. In the meantime, Maurice Wilkins' friend Francis Crick had joined forces with James Watson under the supervision of Max Perutz at the Cavendish Laboratory, Cambridge and under the overall direction of Lawrence Bragg.

## DNA

At King's College Wilkins pursued, among other things x-ray diffraction work on DNA that had been obtained from calf thymus by the Swiss scientist Rudolf Signer. The DNA from Signer's lab was much more intact than the DNA which had previously been isolated. Wilkins discovered that it was possible to produce thin threads from this concentrated DNA solution that contained highly ordered arrays of DNA suitable for the production of x-ray diffraction patterns.<sup>[3]</sup> Using a carefully bundled group of these DNA threads and keeping them hydrated, Wilkins and a graduate student Raymond Gosling obtained x-ray photographs of DNA that showed that the long, thin DNA molecule in the sample from Signer had a regular, crystal-like structure in these threads. This initial x-ray diffraction work at Kings College was done in May or June 1950. It was one of the x-ray diffraction photographs taken in 1950, shown at a meeting in Naples a year later, that sparked James Watson's interest in DNA.

At that time Wilkins also introduced Francis Crick to the importance of DNA. Wilkins knew that proper experiments on the threads of purified DNA would require better x-ray equipment. Wilkins ordered a new x-ray tube and a new microcamera. Before the DNA sample from Signer was available, Gosling had been trying to make x-ray diffraction images of sperm. However, Franklin did not start using the new equipment until September 1951. By the summer of 1950 Randall had arranged for a three year research fellowship that would fund Rosalind Franklin in his laboratory. Franklin was delayed in finishing her work in Paris. Late in 1950, Randall wrote to Franklin to inform her that rather than work on protein, she should take advantage of Wilkins's preliminary work and that she should do x-ray studies of DNA fibers made from Signer's samples of DNA. Early in 1951 Franklin finally arrived. Wilkins was away on holiday and missed an initial meeting at which Raymond Gosling stood in for him along with Alex Stokes, who, like Crick, would solve the basic mathematics that make possible a general theory of how helical structures diffract x-rays. No work had been done on DNA in the laboratory for several months; the new x-ray tube sat unused, waiting for Franklin. Franklin ended up with the DNA from Signer, Gosling became her PhD student, and she had the expectation that DNA x-ray diffraction work was her project. Wilkins returned to the laboratory expecting that Franklin would be his collaborator and that they would work together on the DNA project that he had started. Franklin felt that DNA was now her project and would not collaborate with Wilkins, who then pursued parallel studies.

By November 1951 Wilkins had evidence that DNA in cells as well as purified DNA had a helical structure.<sup>[4]</sup> Alex Stokes had solved the basic mathematics of helical diffraction theory and thought that Wilkins's x-ray diffraction data indicated a helical structure in DNA. Wilkins met with Watson and Crick and told them about his results. This information from Wilkins, along with additional information gained by Watson when he heard Franklin talk about her research during a King's College research meeting, stimulated Watson and Crick to create their first molecular model of DNA, a model with the phosphate backbones at the center. Upon viewing the model of the proposed structure, Franklin told Watson and Crick that it was wrong. Franklin knew from basic chemical principles the hydrophilic backbones should go on the outside of the molecule where they could interact with water. Crick tried to



get Wilkins to continue with additional molecular modeling efforts, but Wilkins did not take this approach. During 1952, Franklin also refused to participate in molecular modeling efforts and continued to work on step-by-step detailed analysis of her x-ray diffraction data (Patterson synthesis). By the spring of 1952, Franklin had received permission from Randall to ask to transfer her fellowship so that she could leave King's College and work in John Bernal's laboratory at Birkbeck College, also in London. However, Franklin remained at King's College for another year.

By early 1953, it was clear that Franklin would simply drop her DNA work at the end of her fellowship that summer, or even sooner due to illness. Linus Pauling had published a proposed but incorrect structure of DNA, making the same basic error that Watson and Crick had made a year earlier. Some of those working on DNA in the United Kingdom feared that Pauling would quickly solve the DNA structure once he recognized his error and put the backbones of the nucleotide chains on the outside of a model of DNA. After March 1952 Franklin concentrated on the x-ray data for the A-form of less hydrated DNA while Wilkins tried to work on the hydrated B-form. Wilkins was handicapped because Franklin had all of the good DNA. Wilkins got new DNA samples, but it was not as good as the original sample he had used in 1950 and which Franklin continued to use. Most of his new results were for biological samples like sperm cells, which seemed to also suggest a helical structure for DNA. In the middle of 1952 Wilkins had for a time abandoned further DNA work when Franklin reported to him that her results made her doubt the helical nature of the A-form. Wilkins feared that the data suggesting a helical structure might just be an artifact.

In early 1953 Watson visited King's College and Wilkins showed him a high quality image of the B-form x-ray diffraction pattern, now nicknamed photo 51, that Franklin had produced in March 1952. With the knowledge that Pauling was working on DNA and had submitted a model of DNA for publication, Watson and Crick mounted one more concentrated effort to deduce the structure of DNA. Through from Max Perutz, his thesis supervisor, Crick gained access to a progress report from King's College that included useful information from Franklin about the features of DNA she had deduced from her x-ray diffraction data. Watson and Crick published their proposed DNA double helical structure in a paper in the journal *Nature* in April 1953. In this paper Watson and Crick acknowledged that they had been "stimulated by.... the unpublished results and ideas" of Wilkins and Franklin.

The discovery itself was made on 28 February 1953 by Watson and Crick; the first Watson-Crick paper appeared in *Nature* on 25 April 1953. Sir Lawrence Bragg, the director of the Cavendish Laboratory, where Watson and Crick worked, gave a talk at Guys Hospital Medical School in London on Thursday 14 May 1953 which resulted in an article by Ritchie Calder in *The News Chronicle* of London, on Friday 15 May 1953, entitled "Why You Are You. Nearer Secret of Life." The news reached readers of *The New York Times* the next day; Victor K. McElheny, in researching his biography of Watson, "Watson and DNA: Making a Scientific Revolution", found a clipping of a six-paragraph *New York Times* article written from London and dated 16 May 1953 with the headline "Form of 'Life Unit' in Cell Is Scanned." The article ran in an early edition and was then pulled to make space for news deemed more important. (The *New York Times* subsequently ran a longer article on 12 June 1953). The Cambridge University undergraduate newspaper *Varsity* also ran its own short article on the discovery on Saturday 30 May 1953. Bragg's original announcement at a Solvay conference on proteins in Belgium on 8 April 1953 went unreported by the press.

In recognition of the contribution from King's College, Watson and Crick agreed that Wilkins, Stokes, and Wilson<sup>[5]</sup> and Franklin and Gosling should each publish their x-ray diffraction work, which supported the proposed Crick-Watson model, in separate articles in the same issue of *Nature*.

Wilkins and others went on to repeat and extend much of Franklin's work, and produced abundant evidence to support the helical model produced by Crick and Watson.

Wilkins married his second wife Patricia Ann Chidgey in 1959. They had four children, Sarah, George, Emily and William; he had a son by his previous marriage, to an art student called Ruth in California.

He published his autobiography, "The Third Man of the Double Helix," in 2003, but does not specifically credit Stokes and Wilson as co-authors of their paper in "Nature". Whether this was deliberate on his part or just the result

of poor sub-editing by the publisher is not known.

## Recognition

In 1960 he was presented with the American Public Health Association's Albert Lasker Award, and in 1962 he was made a Commander of the British Empire. Also in 1962 he shared the Nobel Prize in Physiology or Medicine with Watson and Crick for the discovery of the structure of DNA.

On Saturday 20 October 1962 the award of Nobel prizes to John Kendrew and Max Perutz, and to Crick, Watson, and Wilkins was satirised in a short sketch in the BBC TV programme *That Was The Week That Was* with the Nobel Prizes being referred to as 'The Alfred Nobel Peace Pools.'

In 2000, King's College London opened the *Franklin-Wilkins Building* in honour of Dr. Franklin's and Professor Wilkins' work at the college.<sup>[6]</sup>

The wording on the new DNA sculpture (which was donated by James Watson) outside Clare College's Thirkill Court, Cambridge, England is

a) on the base:

- i) "These strands unravel during cell reproduction. Genes are encoded in the sequence of bases."
- ii) "The double helix model was supported by the work of Rosalind Franklin and Maurice Wilkins."

b) on the helices:

- i) "The structure of DNA was discovered in 1953 by Francis Crick and James Watson while Watson lived here at Clare."
- ii) "The molecule of DNA has two helical strands that are linked by base pairs Adenine - Thymine or Guanine - Cytosine."

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A plaque commemorating Maurice Wilkins and his discovery, beneath the monument, Pongaroa, New Zealand

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- Ridley, Matt; "Francis Crick: Discoverer of the Genetic Code (Eminent Lives)" was first published in June 2006 in the USA and then in the UK September 2006, by HarperCollins Publishers; 192 pp, ISBN 0-06-082333-X; this short book is in the publisher's "Eminent Lives" series.
- "Light Is A Messenger, the life and science of William Lawrence Bragg" by Graeme Hunter, ISBN 0-19-852921-X; Oxford University Press, 2004.
- "Designs For Life: Molecular Biology After World War II" by Soraya De Chadarevian; CUP 2002, 444 pp; ISBN 0-521-57078-6; it includes James Watson's "well kept open secret" from April 2003!
- Tait, Sylvia & James "A Quartet of Unlikely Discoveries" (Athena Press 2004) ISBN 184401343X

## External links

- (<http://www.independent.co.uk/news/obituaries/professor-maurice-wilkins-543103.html>) Obituary from The Independent on Sunday, 9 October 2004.
- (<http://orpheus.ucsd.edu/speccoll/testing/html/mss0660a.html#abstract>) Crick's personal papers at Mandeville Special Collections Library, Geisel Library, University of California, San Diego
- "Quiet debut for the double helix" (<http://chem-faculty.ucsd.edu/joseph/CHEM13/DNA1.pdf>) by Professor Robert Olby, *Nature* **421** (January 23, 2003): 402-405.
- (<http://www.peoplesarchive.com/>) for the People's Archive/BBC 90 story interview with Crick AND the 236 story interview with Brenner.
- (<http://nobelprize.org/medicine/laureates/1962/press.html>) Presentation speech at the Nobel Prize ceremony in 1962.

- Reading University site on 50th anniversary of Discovery of the structure of DNA (<http://www.ncbe.reading.ac.uk/DNA50/reviews.html>). Includes a list of Books (<http://www.ncbe.reading.ac.uk/DNA50/reviews.html>) on the subject.
  - Biography (from Nobel) (<http://www.nobel.se/medicine/laureates/1962/wilkins-bio.html>)
  - Biography (from the New Zealand Edge) (<http://www.nzedge.com/heroes/wilkins.html>)
  - Discovery Story in BA Magazine (<http://www.ba-education.demon.co.uk/for/science/dnamain.html>)
  - DNA: The King's Story detailing Wilkins' involvement in elucidating the structure of DNA (<http://www.kcl.ac.uk/depsta/iss/archives//dna/>)
  - List of classic papers in *Nature* on DNA structure (<http://www.nature.com/nature/dna50/archive.html>)
  - Listen to Francis Crick and James Watson talking on the BBC (<http://www.bbc.co.uk/bbcfour/audiointerviews/profilepages/crickwatson1.shtml>)
  - (<http://www.nytimes.com/packages/pdf/science/dna-article.pdf>) - for reproduction of the original text in June 1953.
  - (<http://www.physicstoday.org/vol-56/iss-3/p42.html>) for Lynne Elkins' article on Franklin.
  - New York Times 50th anniversary series (<http://www.nytimes.com/indexes/2003/02/25/health/genetics/index.html>) of excellent articles.
  - (<http://www.nytimes.com/packages/pdf/science/dna-article.pdf>) The first American newspaper coverage of the discovery of the DNA structure: Saturday, June 13, 1953 The New York Times
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# Rosalind Franklin

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| Rosalind Franklin                                                                                      |                                                                                                                                                                   |
|--------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <br>Rosalind Franklin |                                                                                                                                                                   |
| <b>Born</b>                                                                                            | Notting Hill, London, United Kingdom                                                                                                                              |
| <b>Died</b>                                                                                            | (aged 37)<br>Chelsea, London, United Kingdom<br>Cancer of the ovary                                                                                               |
| <b>Nationality</b>                                                                                     | British                                                                                                                                                           |
| <b>Fields</b>                                                                                          | X-ray crystallography                                                                                                                                             |
| <b>Institutions</b>                                                                                    | British Coal Utilisation Research Association<br><i>Laboratoire central des services chimiques de l'État</i><br>King's College London<br>Birkbeck College, London |
| <b>Alma mater</b>                                                                                      | Newnham College, Cambridge                                                                                                                                        |
| <b>Known for</b>                                                                                       | Fine structure of coal and graphite, DNA structure, viruses                                                                                                       |

**Rosalind Elsie Franklin** (25 July 1920 – 16 April 1958) was a British biophysicist, physicist, chemist, biologist and X-ray crystallographer who made important contributions to the understanding of the fine molecular structures of DNA, RNA, viruses, coal and graphite.

Franklin is still best known for her work on the X-ray diffraction images of DNA. Her data, according to Francis Crick, was "the data we actually used"<sup>[1]</sup> to formulate Crick and Watson's 1953 hypothesis regarding the structure of DNA.<sup>[2]</sup> Furthermore, unpublished drafts of her papers (written as she was arranging to leave the unsupportive research situation at King's College London) show that she had indeed determined the overall B-form of the DNA helix. However, her work was published third, in the series of three DNA *Nature* articles, led by the paper of Watson and Crick which only vaguely acknowledged her evidence in support of their hypothesis.<sup>[3]</sup> The possibility of Franklin having played a major role was not revealed until Watson wrote his personal account, *The Double Helix*,<sup>[4]</sup> which subsequently inspired several people to investigate DNA history and Franklin's contribution. The first, Robert Olby's "The Path to the Double Helix", supplied information about original source materials for those that followed.<sup>[5]</sup> After finishing her portion of the DNA work, Franklin led pioneering work on the tobacco mosaic and polio viruses.

She died at the age of 37 from complications arising from ovarian cancer.

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## Background

Franklin was born in Notting Hill, London<sup>[6]</sup> into an affluent and influential British-Jewish family.<sup>[7]</sup> Her father was Ellis Arthur Franklin (1894–1964), a London merchant banker and her mother was Muriel Frances Waley (1894–1976); she was the elder daughter and second of the family of five children.

Her uncle was Herbert Samuel (later Viscount Samuel) who was Home Secretary in 1916 and the first practicing Jew to serve in the British Cabinet.<sup>[8]</sup> He was also the first High Commissioner (effectively governor) for the British Mandate of Palestine.

Her aunt Helen Carolin Franklin was married to Norman de Mattos Bentwich, who was Attorney General in the British Mandate of Palestine.<sup>[9]</sup> She was active in trade union organisation and women's suffrage, and was later a member of the London County Council.<sup>[10] [11]</sup>

Franklin was educated at St Paul's Girls' School and North London Collegiate School<sup>[12] [13]</sup> where she excelled in science, Latin<sup>[14]</sup> and sports.<sup>[15]</sup> Her family was actively involved with a Working Men's College, where Ellis Franklin, her father, taught electricity, magnetism and the history of the Great War in the evenings and later became vice principal.<sup>[16] [17]</sup> Later Franklin's family helped settle Jewish refugees from Europe who had escaped the Nazis.<sup>[11]</sup>

In the winter of 1938 Franklin went to Newnham College, Cambridge. She passed her finals in 1941, but was only awarded a degree titular, as women were not entitled to degrees (BA Cantab.) from Cambridge at the time; in 1945 Franklin received her PhD from Cambridge University.

## British Coal Utilisation Research Association

Franklin worked for Ronald Norrish between 1941 and 1942. Because of her desire to contribute to the World War II effort, she worked at the British Coal Utilisation Research Association in Kingston-upon-Thames from August 1942, studying the porosity of coal. Her work helped spark the idea of high-strength carbon fibres and was the basis of her 1945 doctoral thesis – "The physical chemistry of solid organic colloids with special reference to coal and related materials".<sup>[18] [19]</sup>

## King's College London

### Double Helix Discovery



William Astbury

Oswald Avery

Francis Crick

Erwin Chargaff

Max Delbrück

Jerry Donohue

Rosalind Franklin

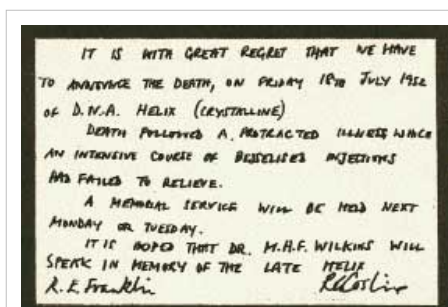
Raymond Gosling

Phoebus Levene  
Linus Pauling  
Sir John Randall  
Erwin Schrödinger  
Alex Stokes  
James Watson  
Maurice Wilkins  
Herbert Wilson

In January 1951, Franklin started working as a research associate at King's College London in the Medical Research Council's (MRC) Biophysics Unit, directed by John Randall.<sup>[20]</sup> Although originally she was to have worked on x-ray diffraction of proteins and lipids in solution, Randall redirected her work to DNA fibers before she started working at King's since Franklin was to be the only experienced experimental diffraction researcher at King's in 1951.<sup>[21] [22]</sup> He made this reassignment, even before she started working at King's, because of the following pioneering work by Maurice Wilkins and Raymond Gosling.<sup>[23]</sup> Even using crude equipment these two men had obtained an outstanding diffraction picture of DNA which sparked further interest in this molecule. Wilkins and Gosling had been carrying out x-ray diffraction analysis of DNA in the Unit since May 1950, but Randall had not informed them of his having asked Franklin to take over both the DNA diffraction work and guidance of Gosling's thesis.<sup>[24]</sup> Randall's lack of communication about this reassignment significantly contributed to the well documented friction that developed between Wilkins and Franklin.<sup>[25]</sup>

Franklin, working with her student Raymond Gosling,<sup>[26]</sup> started to apply her expertise in x-ray diffraction techniques to the structure of DNA. She used a new fine focus x-ray tube and microcamera ordered by Wilkins, but which she refined, adjusted and focused carefully. Drawing upon her physical chemistry background, Franklin also skillfully manipulated the critical hydration of her specimens.<sup>[27]</sup> When Wilkins inquired about this improved technique, Franklin replied in terms which offended Wilkins as Franklin had "an air of cool superiority".<sup>[28]</sup> Franklin's habit of intensely looking people in the eye while being concise, impatient and directly confrontational to the point of abrasiveness unnerved many of her colleagues. In stark contrast, Wilkins was very shy, and slowly calculating in speech while he avoided looking anyone directly in the eye.<sup>[29]</sup> In spite of the intense atmosphere, Franklin and Gosling discovered that there were two forms of DNA: at high humidity (when wet) the DNA fibre became long and thin, when it was dried it became short and fat.<sup>[30] [31]</sup> These were termed DNA 'B' and 'A' respectively. Because of the intense personality conflict developing between Franklin and Wilkins, Randall<sup>[32]</sup> divided the work on DNA. Franklin chose the data rich A form while Wilkins selected the 'B' form<sup>[33] [34]</sup> because his preliminary pictures had hinted it might be helical. He showed tremendous insight in this assessment of preliminary data. The x-ray diffraction pictures taken by Franklin at this time have been called, by J. D. Bernal, "amongst the most beautiful x-ray photographs of any substance ever taken".<sup>[30]</sup>

By the end of 1951 it was generally accepted in King's that the B form of DNA was a helix, but Franklin became unconvinced that the A form of DNA was helical in structure<sup>[35]</sup> after she had recorded an asymmetrical image in 1952 May. As a practical joke on Wilkins (who frequently expressed his view that DNA was helical), Franklin and Gosling produced a death notice regretting the 'death' of helical crystalline DNA (A-DNA).<sup>[36]</sup> During 1952 Rosalind Franklin and Raymond Gosling worked at applying the Patterson function to the x-ray pictures of DNA they had produced.<sup>[37]</sup> This was a long and labour-intensive approach but would yield significant insight into the structure of the molecule.<sup>[38] [39]</sup>



Franklin and Gosling death notice for a helical structure for crystalline DNA (or A-DNA)

By January 1953, Franklin had reconciled her conflicting data and had started to write a series of three draft manuscripts, two of which included a double helical DNA backbone (see below). Her two A form manuscripts reached *Acta Crystallographica* in Copenhagen on 6 March 1953,<sup>[40]</sup> one day before Crick and Watson had completed their model.<sup>[41]</sup> Franklin had to have mailed them while the Cambridge team was building their model, and certainly had written them before she knew of their work. On 8 July, 1953 she modified one of these "in proof", *Acta* articles "in light of recent work" by the King's and Cambridge research teams.<sup>[42]</sup> The third draft paper on the 'B' form of DNA, dated 17 January 1953, was discovered years later amongst her

papers, by Franklin's Birkbeck colleague, Aaron Klug. He then published an evaluation of the draft's close correlation with the third of the original trio of 25 April 1953 *Nature* DNA articles.<sup>[43]</sup> Klug designed this paper to complement the first article he had written defending Franklin's significant contribution to DNA structure.<sup>[44]</sup> He had written this first article in response to the incomplete picture of Franklin's work depicted in Watson's 1968 memoir, *The Double Helix*.

As vividly described in *The Double Helix*, on 30 January 1953, Watson traveled to King's carrying a preprint of Linus Pauling's incorrect proposal for DNA structure. Since Wilkins was not in his office, Watson went to Franklin's lab with his urgent message that they should all collaborate before Pauling discovered his error. The unimpressed Franklin became angry when Watson suggested she did not know how to interpret her own data. Watson hastily retreated, backing into Wilkins who had been attracted by the commotion. Wilkins commiserated with his harried friend and then changed the course of DNA history with the following disclosure. Watson was shown (by Wilkins) Franklin's famous photograph 51, which had been given to Wilkins by Gosling. Watson, in turn, showed Wilkins a pre-publication manuscript by Pauling and Corey.<sup>[45]</sup> Franklin and Gosling's photo 51 gave the Cambridge pair critical insights into the DNA structure, whereas Pauling and Corey's paper described a molecule remarkably like their first incorrect model.

In February 1953 Francis Crick and James D. Watson of the Cavendish Laboratory in Cambridge University had started to build a model of the B form of DNA using similar data to that available to both teams at King's. Much of their data were derived directly from research done at King's by Wilkins and Franklin, with Franklin's being the most unique and critical data completed by February 1953.<sup>[46]</sup> Model building had been applied successfully in the elucidation of the structure of the alpha helix by Linus Pauling in 1951,<sup>[33]</sup> <sup>[47]</sup> but Franklin was opposed to prematurely building theoretical models, until sufficient data was obtained properly to guide the model building. She took the view that building a model was to be undertaken only after enough of the structure was known.<sup>[35]</sup> <sup>[48]</sup> Ever cautious she wanted to eliminate misleading possibilities. Photographs of her Birkbeck work table<sup>[49]</sup> show that she routinely used small molecular models, although certainly not ones on the grand scale successfully used at Cambridge for DNA. In the middle of February 1953, Crick's thesis advisor, Max Perutz gave Crick a copy of a report written for a Medical Research Council biophysics committee visit to King's in December 1952, containing many of Franklin's crystallographic calculations.<sup>[50]</sup> Since Franklin had decided to transfer to Birkbeck College and Randall had insisted that all DNA work must stay at King's, Wilkins was given copies of Franklin's diffraction photographs by Gosling. By 28 February 1953 Watson and Crick felt they had solved the problem enough for Crick to proclaim (in the local pub) that they had "found the secret of life".<sup>[51]</sup> However they knew they must complete their model before they could be certain.<sup>[52]</sup>

Watson and Crick finished building their model on 7 March 1953, one day before they received a letter from Wilkins stating that Franklin was finally leaving and they could put "all hands to the pump".<sup>[53]</sup> This was also one day after Franklin's two A form papers had reached *Acta Crystallographica*. Wilkins came to see the model the following week, according to Maddox on 12 March, and allegedly informed Gosling on his return to King's.<sup>[54]</sup> It is uncertain how



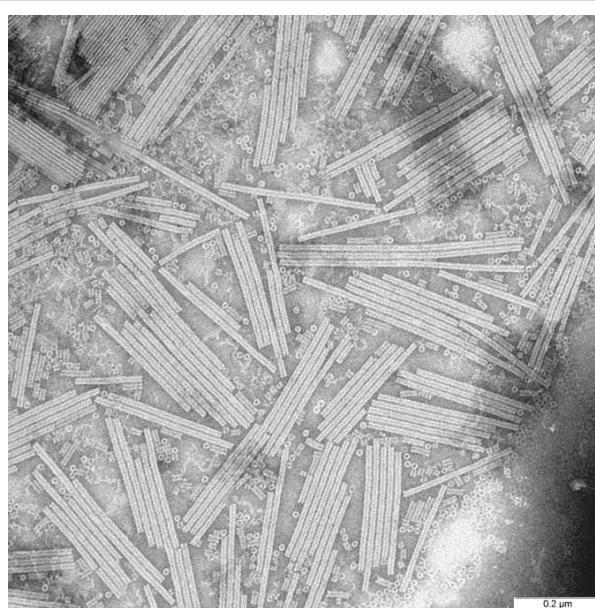
long it took for Gosling to inform Franklin at Birkbeck, but her original 17 March B form manuscript does not reflect any knowledge of the Cambridge model. Franklin did modify this draft later before publishing it as the third in the trio of 25 April 1953 *Nature* articles. On 18 March,<sup>[55]</sup> in response to receiving a copy of their preliminary manuscript, Wilkins penned the following "I think you're a couple of old rogues, but you may well have something".<sup>[56]</sup>

Crick and Watson then published their model in *Nature* on 25 April 1953 in an article describing the double-helical structure of DNA with only a footnote acknowledging "having been stimulated by a general knowledge of" Franklin and Wilkin's 'unpublished' contribution.<sup>[57]</sup> Actually, although it was the bare minimum, they had just enough specific knowledge of Franklin and Gosling's data upon which to base their model. As a result of a deal struck by the two laboratory directors, articles by Wilkins and Franklin, which included their x-ray diffraction data, were modified and then published second and third in the same issue of *Nature*, seemingly only in supported of the Crick and Watson theoretical paper which proposed a model for the B form of DNA.<sup>[58]</sup> <sup>[59]</sup> Franklin left King's College London in March 1953 to move to Birkbeck College in a move that had been planned for some time.<sup>[37]</sup>

Weeks later, on 10 April, Franklin wrote to Crick for permission to see their model.<sup>[60]</sup> Franklin retained her scepticism for premature model building even after seeing the Crick–Watson model, and remained unimpressed. She is reported to have commented, "It's very pretty, but how are they going to prove it?" As an experimental scientist Franklin seems to have been interested in producing far greater evidence before publishing-as-proven a proposed model. As such her response to the Crick–Watson model was in keeping with her cautious approach to science.<sup>[61]</sup> However, as documented above, she did not hesitate to publish preliminary ideas about DNA in ACTA, even before they could be definitively proven. Most of the scientific community hesitated several years before accepting the double helix proposal. At first mainly geneticists embraced the model because of its obvious genetic implications. Broader acceptance for the DNA double helix did not start until about 1960, and was not openly acknowledged until 1961 during the 1962 Nobel prize nominations. It took Wilkins and his colleagues approximately seven years to collect enough data to prove and refine the proposed DNA structure. According to the 1961 Crick–Monod letter cited above, this experimental proof, along with Wilkins having initiated the DNA diffraction work, were the reasons why Crick felt that Wilkins should be included in the DNA Nobel prize.

## Birkbeck College

Franklin work in Birkbeck involved the use of x-ray crystallography to study the structure of the tobacco mosaic virus (TMV) as a senior scientist with her own research group, funded by the Agricultural Research Council (ARC).<sup>[62]</sup> She was recruited by physics department chair J. D. Bernal<sup>[63]</sup>, a brilliant crystallographer who happened to be an Irish communist, known for promoting women crystallographers. In 1954 Franklin began a longstanding and successful collaboration with Aaron Klug.<sup>[64]</sup> In 1955 Franklin had a paper published in the journal *Nature*, indicating that TMV virus particles were all of the same length,<sup>[65]</sup> this was in direct contradiction to the ideas of the eminent virologist Norman Pirie, though her observation ultimately proved correct.<sup>[66]</sup>



Electronmicrograph of Tobacco Mosaic Virus

Franklin, and the research group she headed, focused on the structure of RNA, a molecule equally central to life as DNA. RNA actually constitutes the genome (central information molecule) of many viruses, including tobacco mosaic virus. She assigned the study of rod-like viruses such as TMV (tobacco mosaic virus) to her PhD student Kenneth Holmes, while her colleague Aaron Klug worked on spherical viruses with his student John Finch, with Franklin coordinating and overseeing the work.<sup>[67]</sup> Franklin also had a research assistant, James Watt, subsidised by the National Coal Board and was now the *Leader of the "ARC group at Birkbeck."*<sup>[68]</sup> By the end of 1955 her team had completed a model of the TMV, to be exhibited at the upcoming Brussels World's fair. The Birkbeck team members were working on RNA viruses affecting several plants, including potato, turnip, tomato and pea.<sup>[69]</sup> Franklin and Don Caspar produced a paper each in *Nature* that taken together demonstrated that the DNA in TMV is wound along the inner surface of the hollow virus.<sup>[70] [71]</sup>

Her former colleagues at Birkbeck College, London Aaron Klug, John Finch and Kenneth Holmes moved to the Laboratory of Molecular Biology, Cambridge in 1962.

## Illness and death

In the summer of 1956, while on a work-related trip to the United States, Franklin first began to suspect a health problem.<sup>[72]</sup> An operation in September of the same year revealed two tumours in her abdomen.<sup>[73]</sup> After this period and other periods of hospitalization, Franklin spent time convalescing with various friends and family members. These included Anne Sayre, Francis Crick, his wife Odile, with whom Franklin had formed a strong friendship,<sup>[74]</sup> and finally with the Roland and Nina Franklin family where Rosalind's nieces and nephews bolstered her spirits. Franklin chose not to stay with her parents because her mother's uncontrollable grief and crying upset her too much. Even while undergoing cancer treatment, Franklin continued to work, and her group continued to produce results, seven papers in 1956 and a further six in 1957.<sup>[75]</sup> In 1957, the group was also working on the polio virus and had obtained funding from the Public Health Service of the National Institutes of Health in the United States for this.<sup>[76]</sup> At the end of 1957, Franklin again fell ill and she was admitted to the Royal Marsden Hospital. She returned to work in January 1958 and she was given a promotion to *Research Associate in Biophysics.*<sup>[77]</sup> She fell ill again on March 30 and died on April 16, 1958, in Chelsea, London,<sup>[78] [79]</sup> of bronchopneumonia, secondary carcinomatosis and carcinoma of the ovary. Exposure to X-ray radiation is sometimes considered a possible factor in her illness. Other members of her family have died of cancer, and the incidence of "female" cancer is known to be disproportionately high among Ashkenazi Jews.<sup>[80]</sup> Her death certificate read: *A Research Scientist, Spinster, Daughter of Ellis Arthur Franklin, a Banker.*<sup>[81]</sup>

## Controversies after death

Various controversies surrounding Rosalind Franklin came to light following her death.

### Sexism at King's College

Rosalind Franklin worked in a research community that acknowledged women as scientists, but was infused with both conscious and unconscious sexism.<sup>[7]</sup> This sexism pervades Watson's memoir, *The Double Helix*, in which he denigrates her work and frequently refers to her in patronizing terms as "Rosy", a name she never used. Much later, Francis Crick acknowledges, "I'm afraid we always used to adopt--let's say, a *patronizing* attitude towards her". Cambridge colleague Peter Cavendish wrote in a letter, "Wilkins is supposed to be doing this work; Miss Franklin is evidently a fool". The one laboratory director who supposedly supported her, John Randall, pointedly told her to "cease to work on the nucleic acid problem" upon her departure from King's.<sup>[7]</sup>

The 1975 biography of Franklin by Anne Sayre (a friend who actually knew Franklin) asserted that Rosalind Franklin was discriminated against because of her gender and that King's, as an institution, was sexist. Among the examples cited in alleging sexist treatment at King's was that while "the male staff at King's lunched in a large, comfortable, rather clubby dining room" the female staff of all ranks "lunched in the student's hall or away from the

premises".<sup>[82]</sup> <sup>[83]</sup> Others recall differently that most of the MRC group typically ate lunch together (including Franklin) in the mixed dining room discussed below.<sup>[84]</sup> There was a dining room for the exclusive use of men (as was the case at other University of London colleges at the time), as well as a mixed-gender dining room that overlooked the River Thames, and many male scientists reportedly refused to use the male-only dining room owing to the preponderance of theologians.<sup>[85]</sup>

Another accusation regarding gender is that the under-representation of women in John Randall's group where only one participant was a woman was due to unfair exclusion.<sup>[86]</sup> In contrast, defenders of the King's College MRC group argue that women were (by the standards of the time) well-represented in the group, representing eight out of thirty-one members of staff,<sup>[87]</sup> or possibly closer to one in three,<sup>[88]</sup> although most were not senior scientists.<sup>[89]</sup>

## Contribution to the model of DNA

Rosalind Franklin's critical contributions to the Crick and Watson model include an X-ray photograph of B-DNA (called photograph 51),<sup>[90]</sup> that was briefly shown to James Watson by Maurice Wilkins in January 1953,<sup>[91]</sup> <sup>[92]</sup> and a report written for an MRC biophysics committee visit to King's in December 1952 which was shown by Dr. Max Perutz at the Cavendish Laboratory to both Crick and Watson. This MRC report contained data from the King's group, including some of Rosalind Franklin's and Raymond Gosling's work, and was given to Francis Crick — who was working on his thesis on haemoglobin structure — by his thesis supervisor Max Perutz, a member of the visiting committee.<sup>[93]</sup> <sup>[94]</sup> Maurice Wilkins had been given photograph 51 by Rosalind Franklin's Ph.D. student Raymond Gosling, because she was leaving King's to work at Birkbeck. There was allegedly nothing untoward in this transfer of data to Wilkins,<sup>[95]</sup> <sup>[96]</sup> since the Director John Randall had insisted that all DNA work belonged exclusively to King's and had instructed Franklin in a letter to even stop thinking about it.<sup>[97]</sup> Also it was implied by Horace Freeland Judson, incorrectly, that Maurice Wilkins had taken the photograph out of Rosalind Franklin's drawer<sup>[98]</sup>. However, the B-DNA X-ray pattern photograph in question was shown to Watson by Wilkins — without Franklin's permission. Likewise Max Perutz saw "no harm" in showing an MRC report containing the conclusions of Franklin and Gosling's X-ray data analysis to Crick, since it had not been marked as confidential, although — in the customary British manner in which everything official is considered secret until it is deliberately made public — the report was not expected to reach outside eyes".<sup>[99]</sup> Indeed after the publication of Watson's *The Double Helix* exposed Perutz's act, he received so many letters questioning his judgement that he felt the need to both answer them all<sup>[100]</sup> and to post a general statement in *Science* excusing himself on the basis of being "inexperienced and casual in administrative matters".<sup>[101]</sup> Perutz also claimed that the MRC information was already made available to the Cambridge team when Watson had attended Franklin's seminar in November 1951. A preliminary version of much of the important material contained in the 1952 December MRC report had been presented by Franklin in a talk she had given in 1951 November, which Dr. Watson had attended but not understood.<sup>[102]</sup> <sup>[103]</sup> The Perutz letter was one of three letters, published with letters by Wilkins and Watson, which discussed their various contributions. Watson clarified the importance of the data obtained from the MRC report as he had not recorded these data while attending Franklin's lecture in 1951. The upshot of all this was that when Crick and Watson started to build their model in February 1953 they were working with critical parameters that had been determined by Franklin in 1951, and which she and Gosling had significantly refined in 1952, as well as with published data and other very similar data to those available at King's. Rosalind Franklin was probably never aware that her work had been used during construction of the model,<sup>[104]</sup> but Maurice Wilkins was.

## Recognition of her contribution to the model of DNA

On the completion of their model, Francis Crick and James Watson had invited Maurice Wilkins to be a co-author of their paper describing the structure.<sup>[105]</sup> <sup>[106]</sup> Wilkins turned down this offer, as he had taken no part in building the model.<sup>[107]</sup> Maurice Wilkins later expressed regret that greater discussion of co-authorship had not taken place as this might have helped to clarify the contribution the work at King's had made to the discovery.<sup>[108]</sup> There is no doubt that Franklin's experimental data were used by Crick and Watson to build their model of DNA in 1953 (see above). Some, including Maddox as cited next, have explained this citation omission by suggesting that it may be a question of circumstance, because it would have been very difficult to cite the unpublished work from the MRC report they had seen.<sup>[109]</sup> Indeed a clear timely acknowledgment would have been awkward, given the unorthodox manner in which data was transferred from King's to Cambridge, however methods were available. Watson and Crick could have cited the MRC report as a personal communication or else cited the ACTA articles in press, or most easily, the third Nature paper that they knew was in press. One of the most important accomplishments of Maddox's widely acclaimed biography is that Maddox made a well-received case for inadequate acknowledgement. "Such acknowledgement as they gave her was very muted and always coupled with the name of Wilkins".<sup>[110]</sup>

Twenty five years after the fact, the first clear recitation of Franklin's contribution appeared as it permeated Watson's account, *The Double Helix*, although it was buried under allegations that Franklin did not know how to interpret her own data and that she should have therefore shared her work with Wilkins, Watson, and Crick. This attitude is epitomized in the confrontation between Watson and Franklin over a pre-print of Pauling's mistaken DNA manuscript.<sup>[111]</sup> Watson's words impelled Sayre to write her rebuttal, in which she designs her entire chapter nine, "Winner Take All" to be like a legal brief dissecting and analyzing the topic of acknowledgment.<sup>[112]</sup> Unfortunately Sayre's early analysis was often ignored because of the supposed feminist overtones in her book. It should be noted that in their original paper, Watson and Crick do cite the X-ray diffraction work of both Wilkins and William Astbury. In addition, they admit their, "having been stimulated by a knowledge of the general nature of the unpublished experimental work of [groups led by both both Wilkins and Franklin]".<sup>[2]</sup> Franklin and Raymond Gosling's own publication in the same issue of *Nature* was the first publication of this more clarified X-ray image of DNA.<sup>[113]</sup>

## Nobel Prize

The rules of the Nobel Prize forbid posthumous nominations<sup>[106]</sup> and because Rosalind Franklin had died in 1958 she was not eligible for nomination to the Nobel Prize subsequently awarded to Crick, Watson, and Wilkins in 1962.<sup>[114]</sup> The award was for their body of work on nucleic acids and not exclusively for the discovery of the structure of DNA.<sup>[115]</sup> By the time of the award Wilkins had been working on the structure of DNA for over 10 years, and had done much to confirm the Watson-Crick model.<sup>[116]</sup> Crick had been working on the genetic code at Cambridge and Watson had worked on RNA for some years.<sup>[117]</sup>

## Posthumous recognition

- 1982, Iota Sigma Pi designated Franklin a National Honorary Member.<sup>[118]</sup>
  - 1992, English Heritage placed a blue plaque on the house Rosalind Franklin grew up in.<sup>[119]</sup>
  - 1993, King's College London rename the Orchard Residence at their Hampstead Campus on Kidderpore Avenue Rosalind Franklin Hall.
  - 1995, Newnham College dedicated a residence in her name and put a bust of her in its garden.<sup>[119]</sup>
- 
- Rosalind Franklin University of Medicine and Science
- 1997, Birkbeck, University of London School of Crystallography opened the Rosalind Franklin laboratory.<sup>[120]</sup>
  - 1998, National Portrait Gallery added Rosalind Franklin's next to those of Francis Crick, James Watson and Maurice Wilkins.<sup>[119] [121]</sup>
  - 2000, King's College London opened the Franklin-Wilkins Building in honour of Dr. Franklin's and Professor Wilkins' work at the college.<sup>[122]</sup> King's had earlier, in 1994, also named one of the Halls in Hampstead Campus residences in memory of Rosalind Franklin.
  - 2001, The U.S. National Cancer Institute established the Rosalind E. Franklin Award for Women in Science.<sup>[123]</sup>
  - 2003, the Royal Society established the Rosalind Franklin Award, for an outstanding contribution to any area of natural science, engineering or technology.<sup>[124]</sup>
  - 2004, Finch University of Health Sciences/The Chicago Medical School, located in North Chicago, IL, changed its name to Rosalind Franklin University of Medicine and Science.<sup>[125]</sup>
  - 2004, The University of Groningen, The Netherlands installed Rosalind Franklin fellowships to promote the hiring of young, promising, female researchers.
  - 2005, the wording on the DNA sculpture (which was donated by James Watson) outside Clare College's Thirkill Court, Cambridge, UK is a) on the base: i) "These strands unravel during cell reproduction. Genes are encoded in the sequence of bases." and ii) "*The double helix model was supported by the work of Rosalind Franklin and Maurice Wilkins.*", as well as b) on the helices: i) "The structure of DNA was discovered in 1953 by Francis Crick and James Watson while Watson lived here at Clare." and ii) "The molecule of DNA has two helical strands that are linked by base pairs Adenine – Thymine or Guanine – Cytosine."<sup>[126]</sup>
  - 2008, Columbia University awarded an Honorary Horwitz Prize to Rosalind Franklin, Ph.D., posthumously, "for her seminal contributions to the discovery of the structure of DNA".<sup>[127]</sup>

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## External links

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# Notable physicists with interests in Biology

## William Lawrence Bragg

### William Lawrence Bragg



William L. Bragg in 1915

|                                                                                                                                                                                                                                   |                                                                   |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| <b>Born</b>                                                                                                                                                                                                                       | 31 March 1890<br>North Adelaide, South Australia                  |
| <b>Died</b>                                                                                                                                                                                                                       | 1 July 1971 (aged 81)<br>Waldringfield, Ipswich, Suffolk, England |
| <b>Nationality</b>                                                                                                                                                                                                                | United Kingdom                                                    |
| <b>Institutions</b>                                                                                                                                                                                                               | University of Manchester<br>University of Cambridge               |
| <b>Alma mater</b>                                                                                                                                                                                                                 | University of Adelaide<br>University of Cambridge                 |
| <b>Doctoral advisor</b>                                                                                                                                                                                                           | J. J. Thomson<br>W.H. Bragg                                       |
| <b>Doctoral students</b>                                                                                                                                                                                                          | John Crank<br>Ronald Wilfried Gurney                              |
| <b>Known for</b>                                                                                                                                                                                                                  | X-ray diffraction<br>Bragg's Law                                  |
| <b>Notable awards</b>                                                                                                                                                                                                             | Nobel Prize in Physics (1915)                                     |
| <b>Notes</b><br>At 25, the youngest person ever to receive a Nobel Prize. He was the son of W.H. Bragg. Note that the PhD did not exist at Cambridge until 1919, and so J. J. Thomson and W.H. Bragg were his equivalent mentors. |                                                                   |

**Sir William Lawrence Bragg**, CH, OBE, MC, FRS (31 March 1890 – 1 July 1971) was an English physicist who shared the Nobel Prize in Physics in 1915 with his father Sir William Henry Bragg. He was the director of the Cavendish Laboratory, Cambridge when the epochal discovery of the structure of DNA was made by James D. Watson and Francis Crick in February 1953.

## Biography

### Early years

Bragg was born in North Adelaide, South Australia. He was an impressionable boy and showed an early interest in science and mathematics. His father, William Henry Bragg, was Elder Professor of Mathematics and Physics at the University of Adelaide. Shortly after starting school aged 5, William Lawrence Bragg fell from his tricycle and broke his arm. His father, who had read about Röntgen's experiments in Europe and was performing his own experiments, used the newly discovered X-rays and his experimental equipment to examine the broken arm. This is the first recorded surgical use of X-rays in Australia.

Bragg was a very able student. After beginning his studies at St Peter's College, in 1904 he went to the University of Adelaide at age 14 to study mathematics, chemistry and physics, graduating in 1908. In the same year his father accepted the Cavendish chair of physics at the University of Leeds, and brought the family back to England. Bragg entered Trinity College, Cambridge in the autumn of 1909 and received a major scholarship in mathematics, despite taking the exam while in bed with pneumonia. After initially excelling in mathematics, he transferred to the physics course in the later years of his studies, and graduated in 1911.

### Career

#### Work on X-ray crystallography

Bragg is most famous for his law on the diffraction of X-rays by crystals. Bragg's law makes it possible to calculate the positions of the atoms within a crystal from the way in which an X-ray beam is diffracted by the crystal lattice. He made this discovery in 1912, during his first year as a research student in Cambridge. He discussed his ideas with his father, who developed the X-ray spectrometer in Leeds. This tool allowed many different types of crystals to be analyzed. The collaboration between father and son led many people to believe that the father had initiated the research, a fact that upset the son.

#### Work on sound ranging

Bragg's research work was interrupted by both World War I and World War II. During both wars he worked on sound ranging methods for locating enemy guns, in this work he was aided by William Sansome Tucker, Harold Roper Robinson and Henry Harold Hemming. For his work during WWI he was awarded the Military Cross (London Gazette, 1 January 1918) and appointed an Officer of the British Empire (London Gazette, 15 March 1918). He was also mentioned in dispatches on 16 June 1916, 4 January 1917 and 7 July 1919.<sup>[1]</sup>

In autumn 1915 his brother was killed at Gallipoli. At about the same time, William Lawrence Bragg received the news that he received the Nobel Prize in Physics, aged 25, making him the youngest ever winner of a Nobel Prize.

Between the wars, from 1919 to 1937, he worked at the Victoria University of Manchester as Langworthy Professor of Physics.

After World War II, he returned to Cambridge, splitting the Cavendish Laboratory into research groups. He believed that "the ideal research unit is one of six to twelve scientists and a few assistants".

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### Work on proteins

In 1948 he became interested in the structure of proteins and was partly responsible for creating a group that used physics to solve biological problems. He played a major part in the 1953 discovery of the structure of DNA, in that he provided support to Francis Crick and James D. Watson who worked under his aegis at the Cavendish.

Bragg's original announcement of the discovery of the structure of DNA was made at a Solvay conference on proteins in Belgium on 8 April 1953 but went unreported by the press, he then gave a talk at Guys Hospital Medical School in London on Thursday, May 14, 1953 which resulted in an article by Ritchie Calder in The News Chronicle of London, on Friday, May 15, 1953, entitled "Why You Are You. Nearer Secret of Life."

Bragg was gratified to see that the X-ray method that he developed forty years before was at the heart of this profound insight into the nature of life itself. At the same time at the Cavendish Max Perutz was also doing his Nobel Prize winning work on the structure of hemoglobin. Bragg subsequently successfully lobbied for and nominated Crick, Watson and Maurice Wilkins for the 1962 Nobel Prize in Physiology or Medicine; Wilkins' share recognized the contribution made by researchers (using X-ray crystallography) at King's College London to the determination of the structure of DNA. Among those researchers was Rosalind Franklin, whose "Photograph 51" showed that DNA was a double helix, not a triple helix as Linus Pauling had proposed. Franklin died before the prize (which only goes to living people) was awarded.

### Personal life

He married Alice Hopkinson in 1921. They had four children, Stephen Lawrence, David William, Margaret Alice and Patience Mary. He died at a hospital near his home at Waldringfield, Ipswich, Suffolk.

William Lawrence Bragg's hobbies included painting, literature and a life-long interest in gardening. When he moved to London, he missed having a garden and so worked as a part-time gardener, unrecognised by his employer, until a guest at the house expressed surprise at seeing him there.

### Honours and awards

He was knighted by King George VI in 1941<sup>[2]</sup> and received both the Copley Medal and the Royal Medal of the Royal Society. In 1967 was made a Companion of Honour by the Queen Elizabeth II.

Since 1992 the Australian Institute of Physics has awarded the Bragg Gold Medal for Excellence in Physics<sup>[3]</sup> to commemorate Sir Lawrence Bragg (in front on the medal) and his father Sir William Bragg for the best PhD thesis by a student at an Australian university.

- Nobel Prize (1915)
  - Matteucci Medal (1915)
  - Hughes Medal (1931)
  - Royal Medal (1946)
  - Copley Medal (1966)
-

## Quotations

"The gift of expression is important to them as scientists; the best research is wasted when it is extremely difficult to discover what it is all about ... It is even more important when scientists are called upon to play their part in the world of affairs, as is happening to an increasing extent."<sup>[4]</sup>

## Books containing references to Sir Lawrence Bragg

- Biography: Hunter, Graeme. *Light Is A Messenger, the Life and Science of William Lawrence Bragg*, ISBN 0-19-852921-X; Oxford University Press, 2004.
- John Finch; 'A Nobel Fellow On Every Floor', Medical Research Council 2008, 381 pp, ISBN 978-1840469-40-0; this book is all about the MRC Laboratory of Molecular Biology, Cambridge.
- Ridley, Matt; *Francis Crick: Discoverer of the Genetic Code (Eminent Lives)*, first published in July 2006 in the USA and then in the UK. September 2006, by HarperCollins Publishers; 192 pp, ISBN 0-06-082333-X; [This short book is in the publisher's "Eminent Lives" series.]
- John Jenkin: "William and Lawrence Bragg, Father and Son: The Most Extraordinary Collaboration in Science", Oxford University Press, 2008.

## See also

- 'Death' of DNA Helix (crystalline) joke funeral card.
- Tactical Artillery Terms from World War I

## External links

- [13] First press stories on DNA
- Nobelprize.org - The Nobel Prize for Physics in 1915 <sup>[5]</sup>
- Nobel Biography <sup>[6]</sup>
- A collection <sup>[7]</sup> of digitized materials related to Bragg's and Linus Pauling's structural chemistry research.
- Key Participants: Sir William Lawrence Bragg <sup>[8]</sup> - *Linus Pauling and the Race for DNA: A Documentary History*
- NOVA Episode on Photograph 51 <sup>[145]</sup>
- Oral History interview transcript with William Lawrence Bragg 20 June 1969, American Institute of Physics, Niels Bohr Library and Archives <sup>[9]</sup>

## References

- [1] William Van der Kloot, Lawrence Bragg's role in the development of sound-ranging in World War I (<http://rsnr.royalsocietypublishing.org/content/59/3/273.full>), Notes and Records of the Royal Society, 22 September 2005, vol. 59, no. 3, pp. 273-284.
- [2] [[http://www.gazettes-online.co.uk/ViewPDF.aspx?London Gazette January 1941](http://www.gazettes-online.co.uk/ViewPDF.aspx?London%20Gazette%20January%201941)] (<http://www.london-gazette.co.uk/issues/35029/supplements/1>)
- [3] <http://www.aip.org.au/content/bragg>
- [4] Gowers, E., *The Complete Plain Words*, Godine, 1988. ISBN 1-56792-203-1.
- [5] [http://nobelprize.org/nobel\\_prizes/physics/laureates/1915/index.html](http://nobelprize.org/nobel_prizes/physics/laureates/1915/index.html)
- [6] [http://nobelprize.org/nobel\\_prizes/physics/laureates/1915/wl-bragg-bio.html](http://nobelprize.org/nobel_prizes/physics/laureates/1915/wl-bragg-bio.html)
- [7] <http://osulibrary.oregonstate.edu/specialcollections/coll/pauling/bond/people/bragg.html>
- [8] <http://osulibrary.oregonstate.edu/specialcollections/coll/pauling/dna/people/bragg.html>
- [9] <http://www.aip.org/history/ohilist/28531.html>

# Nevill Francis Mott

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| Nevill Francis Mott                                                               |                                                                                            |
|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|
|  |                                                                                            |
| <b>Born</b>                                                                       | 30 September 1905<br>Leeds, England                                                        |
| <b>Died</b>                                                                       | 8 August 1996 (aged 90)<br>Milton Keynes, Buckinghamshire, England                         |
| <b>Nationality</b>                                                                | United Kingdom                                                                             |
| <b>Fields</b>                                                                     | Physics                                                                                    |
| <b>Institutions</b>                                                               | University of Manchester<br>Gonville and Caius College, Cambridge<br>University of Bristol |
| <b>Alma mater</b>                                                                 | St John's College, Cambridge                                                               |
| <b>Notable awards</b>                                                             | Nobel Prize in Physics (1977)                                                              |

**Sir Nevill Francis Mott**, CH, FRS (30 September 1905 – 8 August 1996) was an English physicist. He won the Nobel Prize for Physics in 1977 for his work on the electronic structure of magnetic and disordered systems. The award was shared with Philip W. Anderson and J. H. Van Vleck, who had pursued independent research.

## Biography

### Early years

Mott was born in Leeds to Lilian Mary Reynolds and Charles Francis Mott. and grew up first in the village of Giggleswick, in the West Riding of Yorkshire, where his father was Senior Science Master at the local school. It was a generally secular childhood. The family moved (due to his father's jobs) first to Staffordshire, then to Chester and finally Liverpool, where his father had been appointed Director of Education. Mott was at first educated at home by his mother, who was a Cambridge Mathematics Tripos graduate. His parents had actually met in the Cavendish Laboratory, when both engaged in Physics research. At ten years of age he began formal education at Clifton College in Bristol, then at St. John's College, Cambridge.

## Career

Mott was appointed to a lectureship at Manchester University in 1929. He returned to Cambridge in 1930 as a Fellow and lecturer of Gonville and Caius College and in 1933 moved to Bristol University as Melville Wills Professor in Theoretical Physics.

In 1948 he became Henry Overton Wills Professor of Physics and Director of the Henry Herbert Wills Physical Laboratory at Bristol. In 1954 he was appointed Cavendish Professor of Physics at Cambridge, a post he held until 1971. Additionally he served as Master of Gonville and Caius College, 1959-1966.

Mott's accomplishments include explaining theoretically the effect of light on a photographic emulsion (see latent image) and outlining the transition of substances from metallic to nonmetallic states (Mott transition). The term Mott insulator is also named for him.

Mott was elected a Fellow of the Royal Society in 1936. Mott served as president of the Physical Society in 1957. In the early 1960s he was chairman of the British Pugwash group. He was knighted in 1962.<sup>[1]</sup> He continued to work until he was about ninety. He was made a Companion of Honour in 1995.

## Personal life

Mott was married to Ruth Eleanor Horder, and had two daughters, Elizabeth and Alice. He died in Milton Keynes in Buckinghamshire.

## Bibliography

- N. F. Mott, *Metal-Insulator Transitions*, second edition (Taylor & Francis, London, 1990). ISBN 0850667836, ISBN 978-0850667837
- N. F. Mott, *A Life in Science*, (Taylor & Francis, London, 1986). ISBN 0850663334, ISBN 978-0850663334

## References

- Brian Pippard, *Nevill Francis Mott*, Physics Today, March 1997, pp. 95 and 96: (pdf)<sup>[2]</sup>.

## External links

- Nobel lecture<sup>[3]</sup> (PDF)
- Sir Nevill Francis Mott<sup>[4]</sup>
- Mott's memories<sup>[5]</sup> University of Bristol (accessed Jan 2006)
- National Cataloguing Unit for the Archives of Contemporary Scientists<sup>[6]</sup> Bath University

## References

- <sup>[1]</sup> <http://www.gazettes-online.co.uk/ViewPDF.aspx?pdf=42552&geotype=London&gpn=2&type=ArchivedIssuePage&all=&exact=Mott&atleast=&similar=>
- <sup>[2]</sup> <http://scitation.aip.org/getpdf/servlet/GetPDFServlet?filetype=pdf&id=PHTOAD000050000003000095000003&idtype=cvips&prog=search>
- <sup>[3]</sup> [http://nobelprize.org/nobel\\_prizes/physics/laureates/1977/mott-lecture.pdf](http://nobelprize.org/nobel_prizes/physics/laureates/1977/mott-lecture.pdf)
- <sup>[4]</sup> [http://www.nobel-winners.com/Physics/nevill\\_francis\\_mott.html](http://www.nobel-winners.com/Physics/nevill_francis_mott.html)
- <sup>[5]</sup> <http://www.phy.bris.ac.uk/history/11.%20Mott's%20Memories.pdf>
- <sup>[6]</sup> <http://www.bath.ac.uk/ncuacs/rsip-nfm.htm>



# Erwin Schrödinger

| Erwin Schrödinger                                                                                |                                                                                                                                                                                                                                               |
|--------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                 |                                                                                                                                                                                                                                               |
| Born                                                                                             | Erwin Rudolf Josef Alexander Schrödinger<br>12 August 1887<br>Erdberg de, Vienna, Austria-Hungary                                                                                                                                             |
| Died                                                                                             | 4 January 1961 (aged 73)<br>Vienna, Austria                                                                                                                                                                                                   |
| Citizenship                                                                                      | Austria, Germany, Ireland                                                                                                                                                                                                                     |
| Nationality                                                                                      | Austria                                                                                                                                                                                                                                       |
| Fields                                                                                           | Physics                                                                                                                                                                                                                                       |
| Institutions                                                                                     | University of Breslau<br>University of Zürich<br>Humboldt University of Berlin<br>University of Oxford<br>University of Graz<br>Dublin Institute for Advanced Studies<br>Ghent University                                                     |
| Alma mater                                                                                       | University of Vienna                                                                                                                                                                                                                          |
| Doctoral advisor                                                                                 | Friedrich Hasenöhl                                                                                                                                                                                                                            |
| Other academic advisors                                                                          | Franz S. Exner<br>Friedrich Hasenöhl                                                                                                                                                                                                          |
| Notable students                                                                                 | Linus Pauling<br>Felix Bloch                                                                                                                                                                                                                  |
| Known for                                                                                        | Schrödinger equation<br>Schrödinger's cat<br>Schrödinger method<br>Schrödinger functional<br>Schrödinger picture<br>Schrödinger-Newton equations<br>Schrödinger field<br>Rayleigh-Schrödinger perturbation<br>Schrödinger logics<br>Cat state |
| Notable awards                                                                                   | Nobel Prize in Physics (1933)                                                                                                                                                                                                                 |
| Signature<br> |                                                                                                                                                                                                                                               |

**Erwin Rudolf Josef Alexander Schrödinger** (German pronunciation: [ˈɛrvɪːn ˈʃrøːdɪŋɐ]; 12 August 1887, Erdberg – 4 January 1961, Vienna) was an Austrian theoretical physicist who achieved fame for his contributions to quantum mechanics, especially the Schrödinger equation, for which he received the Nobel Prize in 1933. In 1935, after extensive correspondence with personal friend Albert Einstein, he proposed the Schrödinger's cat thought experiment.

## Biography

### Early years

In 1887 Schrödinger was born in Vienna, Austria to **Rudolf Schrödinger** (cercloth producer, botanist) and **Georgine Emilia Brenda** (daughter of **Alexander Bauer**, Professor of Chemistry, k.u.k. Technische Hochschule Vienna).

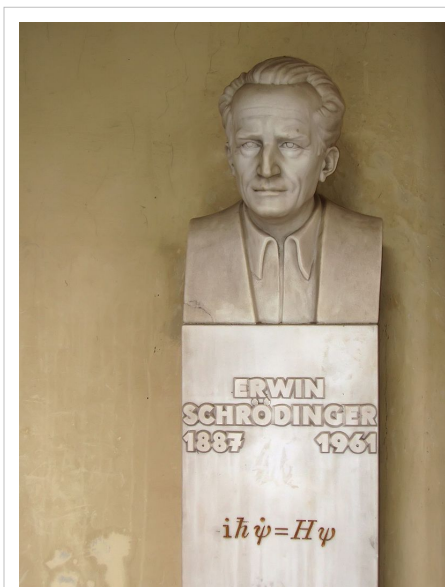
His mother was half Austrian and half English; the English side of her family came from Leamington Spa. Schrödinger learned English and German almost at the same time due to the fact that both were spoken in the family household. His father was a Catholic and his mother was a Lutheran.

In 1898 he attended the Akademisches Gymnasium. Between 1906 and 1910 Schrödinger studied in Vienna under Franz Serafin Exner (1849 - 1926) and Friedrich Hasenöhl (1874 - 1915). He also conducted experimental work with K.W.F. Kohlrausch.<sup>[1]</sup> In 1911, Schrödinger became an assistant to Exner. At an early age, Schrödinger was strongly influenced by Schopenhauer<sup>[2]</sup>. As a result of his extensive reading of Schopenhauer's works, he became deeply interested throughout his life in color theory, philosophy<sup>[3]</sup>, perception, and eastern religion, especially Hindu Vedanta.

### Middle years

In 1914 Erwin Schrödinger achieved Habilitation (*venia legendi*). Between 1914 and 1918 he participated in war work as a commissioned officer in the Austrian fortress artillery (Gorizia, Duino, Sistiana, Prosecco, Vienna). On 6 April 1920, Schrödinger married Annemarie Bertel. The same year, he became the assistant to Max Wien, in Jena, and in September 1920 he attained the position of ao. Prof. (*Ausserordentlicher Professor*), roughly equivalent to Reader (UK) or associate professor (US), in Stuttgart. In 1921, he became o. Prof. (*Ordentlicher Professor*, i.e. full professor), in Breslau (now Wrocław, Poland).

In 1921, he moved to the University of Zürich. In January 1926, Schrödinger published in the *Annalen der Physik* the paper "*Quantisierung als Eigenwertproblem*" [*tr.* Quantization as an Eigenvalue Problem] on wave mechanics and what is now known as the Schrödinger equation. In this paper he gave a "derivation" of the wave equation for time independent systems, and showed that it gave the correct energy eigenvalues for the hydrogen-like atom. This paper has been universally celebrated as one of the most important achievements of the twentieth century, and created a revolution in quantum mechanics, and indeed of all physics and chemistry. A second paper was submitted just four weeks later that solved the quantum harmonic oscillator, the rigid rotor and the diatomic molecule, and gives a new derivation of the Schrödinger equation. A third paper in May showed the equivalence of his approach to that of Heisenberg and gave the treatment of the Stark effect. A fourth paper in this most remarkable series showed how to treat problems in which the system changes with time, as in scattering problems. These papers were the central achievement of his career and were at once recognized as having great significance by the physics community.



Bust of Schrödinger, in the courtyard arcade of the main building, University of Vienna, Austria.

In 1927, he succeeded Max Planck at the Friedrich Wilhelm University in Berlin. In 1933, however, Schrödinger decided to leave Germany; he disliked the Nazis' anti-semitism. He became a Fellow of Magdalen College at the University of Oxford. Soon after he arrived, he received the Nobel Prize together with Paul Adrien Maurice Dirac. His position at Oxford did not work out; his unconventional personal life (Schrödinger lived with two women) was not met with acceptance. In 1934, Schrödinger lectured at Princeton University; he was offered a permanent position there, but did not accept it. Again, his wish to set up house with his wife and his mistress may have posed a problem. He had the prospect of a position at the University of Edinburgh but visa delays occurred, and in the end he took up a position at the University of Graz in Austria in 1936.

In the midst of these tenure issues in 1935, after extensive correspondence with personal friend Albert Einstein, he proposed the Schrödinger's cat thought experiment.

## Later years

In 1939, after the Anschluss, Schrödinger had problems because of his flight from Germany in 1933 and his known opposition to Nazism. He issued a statement recanting this opposition (he later regretted doing so, and he personally apologized to Einstein). However, this did not fully appease the new dispensation and the university dismissed him from his job for political unreliability. He suffered harassment and received instructions not to leave the country, but he and his wife fled to Italy. From there he went to visiting positions in Oxford and Ghent Universities.

In 1940 he received an invitation to help establish an Institute for Advanced Studies in Dublin, Ireland. He moved to Clontarf, Dublin and became the Director of the School for Theoretical Physics and remained there for 17 years, during which time he became a naturalized Irish citizen. He wrote about 50 further publications on various topics, including his explorations of unified field theory.

In 1944, he wrote *What is Life?*, which contains a discussion of Negentropy and the concept of a complex molecule with the genetic code for living organisms. According to James D. Watson's memoir, *DNA, the Secret of Life*, Schrödinger's book gave Watson the inspiration to research the gene, which led to the discovery of the DNA double helix structure. Similarly, Francis Crick, in his autobiographical book *What Mad Pursuit*, described how he was influenced by Schrödinger's speculations about how genetic information might be stored in molecules. However, the geneticist and 1946 Nobel-prize winner H.J. Muller had in his 1922 article "Variation due to Change in the Individual Gene"<sup>[4]</sup> already laid out all the basic properties of the heredity molecule that Schrödinger derives from first principles in *What is Life?*, properties which Muller refined in his 1929 article "The Gene As The Basis of Life"<sup>[5]</sup> and further clarified during the 1930s, long before the publication of *What is Life?*<sup>[6]</sup>.

Schrödinger stayed in Dublin until retiring in 1955. During this time he remained committed to his particular passion; involvements with students occurred and he fathered two children by two different Irish women. He had a life-long interest in the Vedanta philosophy of Hinduism, which influenced his speculations at the close of *What is Life?* about the possibility that individual consciousness is only a manifestation of a unitary consciousness pervading the universe.<sup>[7]</sup>

In 1956, he returned to Vienna (chair *ad personam*). At an important lecture during the World Energy Conference he refused to speak on nuclear energy because of his skepticism about it and gave a philosophical lecture instead. During this period Schrödinger turned from mainstream quantum mechanics' definition of wave-particle duality and promoted the wave idea alone causing much controversy.



Erwin Schrödinger in 1933

## Personal life

Schrödinger suffered from tuberculosis and several times in the 1920s stayed at a sanatorium in Arosa. It was there that he discovered his wave equation.<sup>[8]</sup>

Schrödinger decided in 1933 that he could not live in a country in which persecution of Jews had become a national policy. Alexander Frederick Lindemann, the head of physics at Oxford University, visited Germany in the spring of 1933 to try to arrange positions in England for some young Jewish scientists from Germany. He spoke to Schrödinger about posts for one of his assistants and was surprised to discover that Schrödinger himself was interested in leaving Germany. Schrödinger asked for a colleague, Arthur March, to be offered a post as his assistant.

The request for March stemmed from Schrödinger's unconventional relationships with women: although his relations with his wife Anny were good, he had had many lovers with his wife's full knowledge (and in fact, Anny had her own lover, Hermann Weyl). Schrödinger asked for March to be his assistant because, at that time, he was in love with March's wife Hilde.

Many of the scientists who had left Germany spent mid-1933 in the Italian province of Bolzano. Here Hilde became pregnant with Schrödinger's child. On 4 November 1933 Schrödinger, his wife and Hilde March arrived in Oxford. Schrödinger had been elected a fellow of Magdalen College. Soon after they arrived in Oxford, Schrödinger heard that, for his work on wave mechanics, he had been awarded the Nobel prize.

In early 1934 Schrödinger was invited to lecture at Princeton University and while there he was made an offer of a permanent position. On his return to Oxford he negotiated about salary and pension conditions at Princeton but in the end he did not accept. It is thought that the fact that he wished to live at Princeton with Anny and Hilde both sharing the upbringing of his child was not found acceptable. The fact that Schrödinger openly had two wives, even if one of them was married to another man, was not well received in Oxford either. Nevertheless, his daughter Ruth Georgie Erica was born there on 30 May 1934.<sup>[9]</sup>

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On 4 January 1961, Schrödinger died in Vienna at the age of 73 of tuberculosis. He left a widow, Anny (born Annemarie Bertel on 3 December 1896, died 3 October 1965), and was buried in Alpbach, Austria.

## Legacy

The philosophical issues raised by Schrödinger's cat are still debated today and remains his most enduring legacy in popular science, while Schrödinger's equation is his most enduring legacy at a more technical level. The huge crater Schrödinger on the far side of the Moon is named after him. The Erwin Schrödinger International Institute for Mathematical Physics<sup>[10]</sup> was established in Vienna in 1993.

In the .hack//G.U. game series, a character with the screen name "Schrodinger" constantly raves about physics, skepticism, the meaning of life, etc.

## Color

One of Schrödinger's lesser-known areas of scientific contribution was his work on color, color perception, and colorimetry (*Farbenmetrik*). In 1920, he published three papers in this area:

- "Theorie der Pigmente von größter Leuchtkraft," *Annalen der Physik*, (4), 62, (1920), 603-622
- "Grundlinien einer Theorie der Farbenmetrik im Tagessehen," *Annalen der Physik*, (4), 63, (1920), 397-426; 427-456; 481-520 (Outline of a theory of color measurement for daylight vision)
- "Farbenmetrik," *Zeitschrift für Physik*, 1, (1920), 459-466 (Color measurement)

The second of these is available in English as "Outline of a Theory of Color Measurement for Daylight Vision" in *Sources of Color Science*, Ed. David L. MacAdam, The MIT Press (1970), 134-182.

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- *Nature and the Greeks and Science and Humanism* Cambridge University Press (1996) ISBN 0521575508.
- *The interpretation of Quantum Mechanics* Ox Bow Press (1995) ISBN 1881987094.
- *Statistical Thermodynamics* Dover Publications (1989) ISBN 0486661016.
- *Collected papers* Friedr. Vieweg & Sohn (1984) ISBN 3700105738.
- *My View of the World* Ox Bow Press (1983) ISBN 0918024307.
- *Expanding Universes* Cambridge University Press (1956).
- *Space-Time Structure* Cambridge University Press (1950) ISBN 0521315204.
- *What is Life?* Macmillan (1946).
- *What is Life? & Mind and Matter* Cambridge University Press (1974) ISBN 052109397X.
- *A Life of Erwin Schrödinger*, Walter J. Moore, Cambridge University Press, Canto Edition (2003) ISBN 0521469341.



Erwin Schrödinger's gravesite

## See also

- Entropy and life
- Schrödinger method
- Schrödinger functional
- List of Austrian scientists
- List of Austrians
- *Quantum Aspects of Life*
- *What is Life?*
- Subject-object problem
- Schrödinger's cat

## External links

- Erwin Schrödinger on an Austrian banknote.<sup>[11]</sup>
- O'Connor, John J.; Robertson, Edmund F., "Erwin Schrödinger"<sup>[12]</sup>, *MacTutor History of Mathematics archive*, University of St Andrews.
- 1927 Solvay video with opening shot of Schrödinger<sup>[13]</sup>
- "*biographie*"<sup>[14]</sup> (in German) or
- "*Biography from the Austrian Central Library for Physics*"<sup>[15]</sup> (in English)
- Encyclopaedia Britannica article on Erwin Schrodinger<sup>[16]</sup>
- Nobel Lectures, Physics 1922-1941, "*Erwin Schrödinger Biography*"<sup>[17]</sup> from NobelPrize.org
- Vallabhan, C. P. Girija, "*Indian influences on Quantum Dynamics*"<sup>[18]</sup> [*ed.* Schrödinger's interest in Vedanta]
- Schrödinger Medal<sup>[19]</sup> of the World Association of Theoretically Oriented Chemists (WATOC)
- *The Discovery of New Productive Forms of Atomic Theory* Nobel Banquet speech<sup>[20]</sup> (in German)
- Quantum Mechanics and Schrodinger's Cat<sup>[21]</sup>
- Annotated bibliography for Erwin Schrodinger from the Alsos Digital Library for Nuclear Issues<sup>[22]</sup>
- Schrödinger and his interest for Hinduism<sup>[23]</sup>
- Critical interdisciplinary review of Schrödinger's "What is life?"<sup>[24]</sup>

(Italian)

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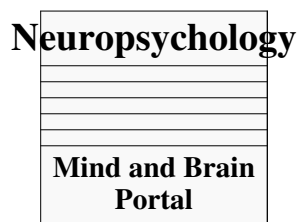
- [1] Karl Grandin, ed. (1933). "Erwin Schrödinger Biography" ([http://nobelprize.org/nobel\\_prizes/physics/laureates/1933/schrodinger-bio.html](http://nobelprize.org/nobel_prizes/physics/laureates/1933/schrodinger-bio.html)). *Les Prix Nobel*. The Nobel Foundation. . Retrieved 2008-07-29.
- [2] *A Life of Erwin Schrödinger*, Chapter 4
- [3] In his lecture "Mind and Matter," Chapter 4, he said that a phrase "that has become familiar to us" is "The world extended in space and time is but our representation (*Vorstellung*)." This is a repetition of the first words of Schopenhauer's main work.
- [4] *American Naturalist* 56 (1922)
- [5] *Proceedings of the International Congress of Plant Sciences* 1 (1929)
- [6] *In Pursuit of the Gene. From Darwin to DNA* - By James Schwartz. Harvard University Press, 2008
- [7] *My View of the World* Erwin Schroedinger chapter iv. What is life? the physical aspect of the living cell & Mind and matter - By Erwin Schrodinger
- [8] *Schrödinger* by Walter J. Moore: Christmas at Arosa ([http://books.google.co.uk/books?id=m-YF1glKWLoC&pg=PA194&lpg=PA194&dq=schrodinger+arosa&source=bl&ots=kC4OC4gfBO&sig=5Sc3QrQBGVpZI94s4tWw9pxXL5I&hl=en&ei=3XYdSuKTIoSsjAf9rIyRDQ&sa=X&oi=book\\_result&ct=result&resnum=4#PPA194,M1](http://books.google.co.uk/books?id=m-YF1glKWLoC&pg=PA194&lpg=PA194&dq=schrodinger+arosa&source=bl&ots=kC4OC4gfBO&sig=5Sc3QrQBGVpZI94s4tWw9pxXL5I&hl=en&ei=3XYdSuKTIoSsjAf9rIyRDQ&sa=X&oi=book_result&ct=result&resnum=4#PPA194,M1))
- [9] *Schrödinger: Life and Thought* by Walter John Moore, Cambridge University Press 1992 ISBN 0-521-43767-9, discusses Schrödinger's unconventional relationships, including his affair with Hildegunde March, in chapters seven and eight, "Berlin" and "Exile in Oxford".
- [10] <http://www.esi.ac.at>
- [11] <http://www-personal.umich.edu/~jbourj/money1.htm>
- [12] <http://www-history.mcs.st-andrews.ac.uk/Biographies/Schrodinger.html>
- [13] <http://uk.youtube.com/watch?v=8GZdZUouzBY>
- [14] <http://www.zbp.univie.ac.at/schrodinger/bio/biol1.htm>

- [15] <http://www.zbp.univie.ac.at/schrodinger/ebio/bio1.htm>
  - [16] <http://www.britannica.com/eb/article-9066219/Erwin-Schrodinger>
  - [17] <http://www.nobel.se/physics/laureates/1933/schrodinger-bio.html>
  - [18] <http://www.photonics.cusat.edu/article2.html>
  - [19] <http://www.ch.ic.ac.uk/watoc>
  - [20] <http://holiker.narod.ru/four/schrodinger-speech.html>
  - [21] <http://www.harrymaugans.com/2006/05/03/in-search-of-schrodingers-cat/>
  - [22] <http://alsos.wlu.edu/qsearch.aspx?browse=people/Schrödinger,+Erwin>
  - [23] [http://www.hinduwisdom.info/quotes21\\_40.htm#Q31](http://www.hinduwisdom.info/quotes21_40.htm#Q31)
  - [24] <http://www.disf.org/CosaDevoSapere/Schroedinger.asp>
-

# David Bohm

| David Bohm                                                                                                                            |                                                                                                                               |
|---------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|
| <div></div> <div>David Joseph Bohm (1917-1992)</div> |                                                                                                                               |
| Born                                                                                                                                  | December 20, 1917<br>Wilkes-Barre, Pennsylvania, U.S.                                                                         |
| Died                                                                                                                                  | October 27, 1992 (aged 74)<br>London, UK                                                                                      |
| Residence                                                                                                                             | United Kingdom                                                                                                                |
| Citizenship                                                                                                                           |  British                                     |
| Nationality                                                                                                                           | British                                                                                                                       |
| Ethnicity                                                                                                                             | Hungarian-Lithuanian Jewish                                                                                                   |
| Fields                                                                                                                                | Physicist                                                                                                                     |
| Institutions                                                                                                                          | Manhattan Project<br>Princeton University<br>University of São Paulo<br>Technion<br>University of Bristol<br>Birkbeck College |
| Alma mater                                                                                                                            | Pennsylvania State College<br>California Institute of Technology<br>University of California, Berkeley                        |
| Doctoral advisor                                                                                                                      | Robert Oppenheimer                                                                                                            |
| Doctoral students                                                                                                                     | Yakir Aharonov<br>David Pines<br>Jeffrey Bub<br>Henri Bortoft                                                                 |
| Other notable students                                                                                                                | Jack Sarfatti                                                                                                                 |
| Known for                                                                                                                             | Bohm-diffusion<br>Bohm interpretation<br>Aharonov-Bohm effect<br>Holonomic model<br>Bohm Dialogue                             |
| Influences                                                                                                                            | Albert Einstein<br>Jiddu Krishnamurti<br>Arthur Schopenhauer<br>Georg Wilhelm Friedrich Hegel                                 |
| Influenced                                                                                                                            | John Stewart Bell                                                                                                             |





**David Joseph Bohm** (20 December 1917 – 27 October 1992) was a U.S.-born British quantum physicist who made significant contributions in the fields of theoretical physics, philosophy and neuropsychology, and to the Manhattan Project.

## Biography

### Youth and college

Bohm was born in Wilkes-Barre, Pennsylvania to a Hungarian Jewish immigrant father and a Lithuanian Jewish mother. He was raised mainly by his father, a furniture store owner and assistant of the local rabbi. Bohm attended Pennsylvania State College, graduating in 1939, and then headed west to the California Institute of Technology for a year, and then transferred to the theoretical physics group under Robert Oppenheimer at the University of California, Berkeley, where he was to obtain his doctorate degree.

Bohm lived in the same neighborhood as some of Oppenheimer's other graduate students (Giovanni Rossi Lomanitz, Joseph Weinberg, and Max Friedman) and with them became increasingly involved not only with physics, but with radical politics. Bohm gravitated to alternative models of society and became active in organizations like the Young Communist League, the Campus Committee to Fight Conscription, and the Committee for Peace Mobilization all later branded as Communist organizations by the FBI under J. Edgar Hoover.

### Work and doctorate

#### Manhattan Project Contributions

During World War II, the Manhattan Project mobilized much of Berkeley's physics research in the effort to produce the first atomic bomb. Though Oppenheimer had asked Bohm to work with him at Los Alamos (the top-secret laboratory established in 1942 to design the bomb), the head of the Manhattan Project, General Leslie Groves, would not approve Bohm's security clearance, after tip-offs about his politics (Bohm's friend, Joseph Weinberg, had also come under suspicion for espionage).

Bohm remained in Berkeley, teaching physics, until he completed his Ph.D. in 1943, under an unusually ironic circumstance. According to Peat (see reference below, p.64), "the scattering calculations (of collisions of protons and deuterons) that he had completed proved useful to the Manhattan Project and were immediately classified. Without security clearance, Bohm was denied access to his own work; not only would he be barred from defending his thesis, he was not even allowed to write his own thesis in the first place!" To satisfy the university, Oppenheimer certified that Bohm had successfully completed the research. He later performed theoretical calculations for the Calutrons at the Y-12 facility in Oak Ridge, used to electromagnetically enrich uranium for use in the bomb dropped on Hiroshima in 1945.

### McCarthyism leads to Bohm leaving the United States

After the war, Bohm became an assistant professor at Princeton University, where he worked closely with Albert Einstein. In May, 1949, at the beginning of the McCarthyism period, the House Un-American Activities Committee called upon Bohm to testify before it—because of his previous ties to suspected Communists. Bohm, however, pleaded the Fifth amendment right to decline to testify, and refused to give evidence against his colleagues.

In 1950, Bohm was charged for refusing to answer questions before the Committee and arrested. He was acquitted in May, 1951, but Princeton had already suspended him. After the acquittal, Bohm's colleagues sought to have his position at Princeton re-instated, and Einstein reportedly wanted Bohm to serve as his assistant. The university, however, did not renew his contract. Bohm then left for Brazil to take up a Chair in Physics at the University of São Paulo, and later was also at the Technion in Haifa, Israel, and at Birkbeck College, University of London.

### Quantum theory and Bohm-diffusion

During his early period, Bohm made a number of significant contributions to physics, particularly in the area of quantum mechanics and relativity theory. As a post-graduate at Berkeley, he developed a theory of plasmas, discovering the electron phenomenon now known as Bohm-diffusion. His first book, *Quantum Theory* published in 1951, was well-received by Einstein, among others. However, Bohm became dissatisfied with the orthodox approach to quantum theory, which he had written about in that book, and began to develop his own approach (Bohm interpretation)—a non-local hidden variable deterministic theory whose predictions agree perfectly with the nondeterministic quantum theory. His work and the EPR argument became the major factor motivating John Bell's inequality, whose consequences are still being investigated.

### The Aharonov-Bohm effect

In 1955 Bohm moved to Israel, where he spent two years at the Technion at Haifa. Here he met his wife Saral, who became an important figure in the development of his ideas. In 1957, Bohm moved to the UK as a research fellow at the University of Bristol. In 1959, with his student Yakir Aharonov, they discovered the Aharonov-Bohm effect, showing how a magnetic field could affect a region of space in which the field had been shielded, although its vector potential did not vanish there. This showed for the first time that the magnetic vector potential, hitherto a mathematical convenience, could have real physical (quantum) effects. In 1961, Bohm was made Professor of Theoretical Physics at Birkbeck College London, where his collected papers<sup>[1]</sup> are kept.

### Bridging science, philosophy, and cognition

Bohm's scientific and philosophical views seemed inseparable. In 1959, his wife Saral recommended to him a book she had seen in the library by the world-renowned speaker on life subjects, Jiddu Krishnamurti. Bohm found himself impressed by the way his own ideas on quantum mechanics meshed with the seemingly-philosophical ideas of Krishnamurti. Bohm's approach to philosophy and physics receive expression in his 1980 book *Wholeness and the Implicate Order*, and in his 1987 book *Science, Order and Creativity*. Bohm and Krishnamurti went on to become close friends for over 25 years, with a deep mutual interest in philosophical subjects and the state of humanity.

### The holonomic model of the brain

Bohm also made significant theoretical contributions to neuropsychology and the development of the holonomic model of the functioning of the brain.<sup>[2]</sup> In collaboration with Stanford neuroscientist Karl Pribram, Bohm helped establish the foundation for Pribram's theory that the brain operates in a manner similar to a hologram, in accordance with quantum mathematical principles and the characteristics of wave patterns. These wave forms may compose hologram-like organizations, Bohm suggested, basing this concept on his application of Fourier analysis, a mathematical method for decomposing complex waves into component sine waves. The holonomic brain model developed by Pribram and Bohm posits a lens defined world view—much like the textured prismatic effect of sunlight refracted by the churning mists of a rainbow—a view which is quite different from the more conventional

"objective reality" - not to be confused with objectivity - approach. Pribram held that if psychology means to understand the conditions that produce the world of appearances, it must look to the thinking of physicists like Bohm.<sup>[3]</sup>

### Thought as a System

Bohm was alarmed by what he considered an increasing imbalance of not only 'man' and nature, but among peoples, as well as people, themselves. Bohm: "So one begins to wonder what is going to happen to the human race. Technology keeps on advancing with greater and greater power, either for good or for destruction." He goes on to ask:

What is the source of all this trouble? I'm saying that the source is basically in thought. Many people would think that such a statement is crazy, because thought is the one thing we have with which to solve our problems. That's part of our tradition. Yet it looks as if the thing we use to solve our problems with is the source of our problems. It's like going to the doctor and having him make you ill. In fact, in 20% of medical cases we do apparently have that going on. But in the case of thought, it's far over 20%.

In Bohm's view:

...the general tacit assumption in thought is that it's just telling you the way things are and that it's not doing anything - that 'you' are inside there, deciding what to do with the info. But you don't decide what to do with the info. Thought runs you. Thought, however, gives false info that you are running it, that you are the one who controls thought. Whereas actually thought is the one which controls each one of us.

Thought is creating divisions out of itself and then saying that they are there naturally. This is another major feature of thought: Thought doesn't know it is doing something and then it struggles against what it is doing. It doesn't want to know that it is doing it. And thought struggles against the results, trying to avoid those unpleasant results while keeping on with that way of thinking. That is what I call "sustained incoherence".

Bohm thus proposes in his book, *Thought as a System*, a pervasive, systematic nature of thought:

What I mean by "thought" is the whole thing - thought, *felt*, the body, the whole society sharing thoughts - it's all one process. It is essential for me not to break that up, because it's all one process; somebody else's thoughts becomes my thoughts, and vice versa. Therefore it would be wrong and misleading to break it up into my thoughts, your thoughts, my feelings, these feelings, those feelings... I would say that thought makes what is often called in modern language a *system*. A system means a set of connected things or parts. But the way people commonly use the word nowadays it means something all of whose parts are mutually interdependent - not only for their mutual action, but for their meaning and for their existence. A corporation is organized as a system - it has this department, that department, that department. They don't have any meaning separately; they only can function together. And also the body is a system. Society is a system in some sense. And so on.

Similarly, thought is a system. That system not only includes thoughts, "felts" and feelings, but it includes the state of the body; it includes the whole of society - as thought is passing back and forth between people in a process by which thought evolved from ancient times. A system is constantly engaged in a process of development, change, evolution and structure changes...although there are certain features of the system which become relatively fixed. We call this the *structure*.... Thought has been constantly evolving and we can't say when that structure began. But with the growth of civilization it has developed a great deal. It was probably very simple thought before civilization, and now it has become very complex and ramified and has much more incoherence than before.

Now, I say that this system has a fault in it - a "systematic fault". It is not a fault here, there or here, but it is a fault that is all throughout the system. Can you picture that? It is everywhere and nowhere. You may say "I see a problem here, so I will bring my thoughts to bear on this problem". But "my" thought is part of the system. It has the same fault as the fault I'm trying to look at, or a similar fault.

Thought is constantly creating problems that way and then trying to solve them. But as it tries to solve them it makes it worse because it doesn't notice that it's creating them, and the more it thinks, the more problems it creates. (P. 18-19)

### Bohm Dialogue

To address societal problems in his later years, Bohm wrote a proposal for a solution that has become known as "Bohm Dialogue", in which equal status and "free space" form the most important prerequisites of communication and the appreciation of differing personal beliefs. He suggested that if these *Dialogue groups* were experienced on a sufficiently wide scale, they could help overcome the isolation and fragmentation Bohm observed was inherent in the society.

### Later years

Bohm continued his work in quantum physics past his retirement in 1987. His final work, the posthumously published *The Undivided Universe: An ontological interpretation of quantum theory* (1993), resulted from a decades-long collaboration with his colleague Basil Hiley. He also spoke to audiences across Europe and North America on the importance of dialogue as a form of sociotherapy, a concept he borrowed from London psychiatrist and practitioner of Group Analysis Patrick De Mare, and had a series of meetings with the Dalai Lama. He was elected Fellow of the Royal Society in 1990.

Near the end of his life, Bohm began to experience a recurrence of depression which he had suffered at earlier times in his life. He was admitted to the Maudsley Hospital in South London on 10 May 1991. His condition worsened and it was decided that the only thing that might help him was electroconvulsive therapy. Bohm's wife consulted psychiatrist David Shainberg, Bohm's long-time friend and collaborator, who agreed that electroconvulsive treatments were probably his only option. Bohm showed marked improvement from the treatments and was released on 29 August. However, his depression returned and was treated with medication.<sup>[4]</sup>

David Bohm died of a heart attack in Hendon,<sup>[5]</sup> London, on 27 October 1992, aged 74. In fact, Professor Bohm was traveling in a London taxi on that day, conversing with the cab driver; and not getting any response from the passenger in the back seat for a few seconds, the driver turned back and found Dr. Bohm had died of a heart attack.<sup>[3]</sup> David Bohm was considered by many Nobel laureates as one of best quantum physicists of all times, who richly deserved the Nobel Prize, but failed to obtain it possibly due to political victimization.<sup>[3]</sup>

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## See also

- Aharonov-Bohm effect
- American philosophy
- Bohm diffusion of a plasma in a magnetic field
- Bohm interpretation
- Correspondence principle
- EPR paradox
- Holographic paradigm
- Holographic principle
- Holomovement
- Holonomic brain theory
- Implicate and Explicate Order
- Implicate order
- Jiddu Krishnamurti
- Membrane paradigm
- Penrose-Hameroff "Orchestrated Objective Reduction" theory of consciousness
- The Bohm sheath criterion, which states that a plasma must flow with at least the speed of sound toward a solid surface
- Wave gene
- John Stewart Bell
- Karl Pribram
- Influence on John David Garcia
- List of American philosophers

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- [2] Comparison between Karl Pribram's "Holographic Brain Theory" and more conventional models of neuronal computation (<http://www.acsa2000.net/bcngroup/jponkp/#chap4>)
- [3] <http://homepages.ihug.co.nz/~sai/pribram.htm>
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## External links

- English site (<http://www.david-bohm.net>) for David Bohm's ideas about Dialogue.
- the David\_Bohm\_Hub ([http://www.thinkg.net/david\\_bohm/](http://www.thinkg.net/david_bohm/)) From thinkg.net, with compilations of David Bohm's life and work in form of texts, audio, video, and pictures.
- Thought Knowledge Perception Institute (<http://www.tkpi.org>) A non-partisan organization that aims to preserve and continue the work of David Bohm and others.
- Lifework of David Bohm: River of Truth ([http://www.vision.net.au/~apaterson/science/david\\_bohm.htm#BOHM'S LEGACY](http://www.vision.net.au/~apaterson/science/david_bohm.htm#BOHM'S%20LEGACY)): Article by Will Keepin
- Dialogos (<http://www.dialogos.com>): Consulting group, originally founded by Bohm colleagues William Isaacs and Peter Garrett, aiming to bring Bohm dialogue into organizations.
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- Interview with David Bohm (<http://www.f davidpeat.com/interviews/bohm.htm>) provided and conducted by F. David Peat along with John Briggs, first issued in *Omni* magazine, January 1987
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- Archive of papers at Birkbeck College relating to David Bohm. (<http://www.bbk.ac.uk/lib/about/hours/bohm>)
- Quantum-Mind (<http://www.quantum-mind.co.uk>)
- Oral History interview transcript with David Bohm 8 May 1981, American Institute of Physics, Niels Bohr Library and Archives (<http://www.aip.org/history/ohilist/4513.html>)

# Ionel Solomon

| Ionel Solomon, PhD.                                                                                                                                  |                                                                                                                                                                                   |
|------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  <p>Member of the French Academy of Sciences since 20 June 1988</p> |                                                                                                                                                                                   |
| <b>Born</b>                                                                                                                                          | 8 January 1929<br>Iași, Romania                                                                                                                                                   |
| <b>Citizenship</b>                                                                                                                                   | French                                                                                                                                                                            |
| <b>Nationality</b>                                                                                                                                   | French                                                                                                                                                                            |
| <b>Fields</b>                                                                                                                                        | physicist                                                                                                                                                                         |
| <b>Alma mater</b>                                                                                                                                    | Paris-Sorbonne University in France                                                                                                                                               |
| <b>Notable awards</b>                                                                                                                                | 1958 Grand Prix for Research (with Anatole Abragam and J. Combrisson); 1963 The CNRS Silver Medal; 1969 Robin Prize of the French Physics Society (Societe Francaise de Physique) |

**Ionel Solomon** (born 1929) is a French-Romanian physicist, Member of the French Academy of Sciences, CNRS Research Director, and Professor at the Polytechnic School in Paris.

## Education

- 1949-1951 PhD, Polytechnic School (École Polytechnique) in Paris

## Major scientific contributions

Ionel Solomon made major contributions to the fields of: Nuclear Magnetic Resonance (NMR)<sup>[1]</sup>, Solid state physics, Semiconductors<sup>[2]</sup> and Photovoltaics<sup>[3]</sup>. In Nuclear Magnetic Resonance he derived fundamental equations that bear his name, and specify the nuclear spin-echo response and dipole-dipole interactions in solids (the *Solomon equations*)<sup>[4]</sup> <sup>[5]</sup>.

## Scientific career

- 1951-1952 Research Fellow at the University of Liverpool, UK
- 1955-1956 Research Fellow at Harvard University, USA
- 1953-1962 Researcher in the resonance Group of the Atomic Energy Commission (Commissariat Energie Atomique in Saclay)
- 1962 Director of the Laboratory for Condensed Matter (Solid-State) Physics (Laboratoire de Physique de la Matière Condensée), at the Polytechnic School in Paris
- 1962 Head of Research at C.N.R.S.
- 1962 Head of Conferences
- 1968 CNRS Research Director
- 1973-1976 Physics Departement Head at the Polytechnic School in Paris 1973-1974 President of the Societé Française de Physique (the French Physics Society).
- 1975-1979 Professor, at the Polytechnic School in Paris
- 1976 Invited Visiting Professor at the Xerox Research Center, Palo Alto, USA

- 1980 Invited Visiting Professor at Tokyo University
- 1981-1985 Founder and Scientific Director of SOLEMS Company
- 1987 President of the Scientific Council of PHOTOTRONICS (a French-German Company for photovoltaic products)
- 1988, June 22, Elected Member of the Physics Institute of the French Academy of Sciences<sup>[6]</sup>
- Laboratory of Condensed Matter Physics

## Awards and prizes

- 1958 Grand Prix for Research (with Anatole Abragam and J. Combrisson)
- 1963 The CNRS Silver Medal
- 1969 Robin Prize of the French Physics Society (Société Française de Physique)
- 1972 Holweck Prize of the Institute of Physics and S.F.P (French Physics Society)
- 1981 The Y. Peyches Prize of the Academy of Sciences

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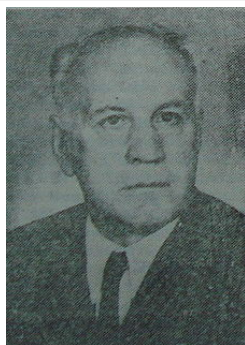


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# Theodor V. Ionescu

## Theodor V. Ionescu



Acad. Prof. Dr. Th. V. Ionescu in Bucharest, 1970

|                    |                                                                                                                                                                                                                                  |
|--------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Born</b>        | February 8, 1899<br>Dorohoi, Romania                                                                                                                                                                                             |
| <b>Died</b>        | November 6, 1988 (aged 89)                                                                                                                                                                                                       |
| <b>Citizenship</b> | Romania                                                                                                                                                                                                                          |
| <b>Ethnicity</b>   | Romanian                                                                                                                                                                                                                         |
| <b>Fields</b>      | physicist                                                                                                                                                                                                                        |
| <b>Alma mater</b>  | Paris-Sorbonne University in France, School of Physics at the University of Iași (currently, Alexandru Ioan Cuza University of Iași), and the University of Bucharest                                                            |
| <b>Known for</b>   | Plasma Physics, magnetic resonance, first maser studies, magnetron invention, 3D cinematography/TV devices, coupled electron-ion oscillations in ultra-hot plasmas and research on nuclear fusion in ultra-hot hydrogen plasmas. |

**Theodor V. Ionescu, Prof. Dr. Doc.** (born February 8 1899, Dorohoi, Botoșani County - d. 6 November 1988, Bucharest) was a Romanian physicist and inventor who made remarkable discoveries in plasma physics, ionosphere physics, ion coupling electrons in dense plasmas, masers, magnetron amplifiers, and Zeeman effects related to controlled nuclear fusion, quantum emission mechanisms in hot plasmas. Member of the Romanian Academy.

## Ph.D. studies in plasma physics

He received his Ph.D. in plasma physics first in Paris, and then in Iași, Romania. Thus, the history of plasma physics in Romania began in 1923 with the defense of the first PhD thesis in physics at the University of Iași by Theodor V. Ionescu, under the guidance of Professor Peter Bogdan. Th. V. Ionescu carried out the first experimental studies in Romania of the physics of ionized gases/plasmas.

## Scientific achievements and collaborators

In 1925 invented a microphone based on thermoionic currents (currents emitted by heated bodies) and a light projector using the interference phenomenon.

*Founded in the same year the first Electricity and Magnetism Laboratory, as well as the first Chair of Electricity and Magnetism in the Department of Mathematics and Physics at the University of Bucharest.*

## The first prototype of a precursor to the magnetron power amplifier

He built in 1934-1935 a precursor<sup>[1]</sup> to the high-power, multi-cavity magnetron that was built subsequently, in 1937-1940, by the British physicist, Sir John Turton Randall, FRSE together with a team of British coworkers for the British and American, military radar instalations in WWII<sup>[2]</sup>. At the same time, the Telefunken Company of Berlin was 'searching' for such a device<sup>[3]</sup> but has apparently met with much less success than the British inventors or Th. V. Ionescu. (However, the split anode magnetron had first been developed in 1921 by Dr. A.E.Hull at GEC Company in USA; also in 1921, Haben, who was working in Germany, developed a similar device that worked on a 3 cm wavelength. A strong competitor of the former inventors was also Dr. H.E.Hollman who registered many patents between 1925 and 1935 that documented devices related to magnetron development)<sup>[4]</sup>.

## Patents

In 1936 he obtained a patent for the 3D imaging in cinema and television. In 1946, together with physicist V. Mihailescu he invented and built a device that has obtained the first 'show boosted " type maser (*microwave quantum amplifier*), and has thus tested the first precursor of the working maser<sup>[5]</sup> reported in 1954<sup>[6]</sup>.

## Discoveries

He worked in the early 1960s in the Laboratory of the Bucharest Institute of Plasma Physics together with his childhood friend, Octav Gheorghiu<sup>[7]</sup>, whom he greatly respected for his exceptional human qualities. They studied systematically the resonant frequencies of molecular oxygen and hydrogen ions. Then, they published their most important experimental results in a series of articles in *C.R. Acad. Sci. Paris*".(pp.245, 898, 957, 246, pp. 2250, 3598, 1958, 250, 2182 p. 1960, 252, p. 870, 1961) and *Rev Roum. Phys.*

In the early 1970s, together with physicists Dr. Radu Pârvan and J. C. Băianu<sup>[8]</sup> - one of his Ph.D. research assistants in plasma physics in magnetic fields in the Electricity Department of the Faculty of Physics, Bucharest - Th. V. Ionescu completed experiments on controlled magnetic resonance oscillations in ultra-hot plasmas. Such seminal experiments involved the coupling of ionic and electronic oscillations in ultra-hot plasma involving quantum amplified stimulation processes in the presence of longitudinal magnetic fields which opened novel possibilities for achieving hot nuclear fusion in the future (Achieving nuclear fusion in high pressure hot plasma<sup>[9]</sup><sup>[10]</sup>). The first report of these research results was presented at the French Academy of Science in Paris by Louis Néel, member of the Academy and Nobel Prize in Physics for Magnetism<sup>[11]</sup>. Additional results were then published in the same year in the internationally renowned magazine *C.R. Acad. Sci. Paris*<sup>[12]</sup>.

His successor as Head of Department in 1970 was Florin Ciorăscu, "imported" from the IFA, (who died in 1977 during the major earthquake in Bucharest).

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- [6] <http://en.wikipedia.org/wiki/Maser>
- [7] [http://alpha1.infim.ro/rrp/2005\\_57\\_1/Gheorghiu.pdf](http://alpha1.infim.ro/rrp/2005_57_1/Gheorghiu.pdf)
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- [9] [http://nobelprize.org/nobel\\_prizes/physics/laureates/1978/kapitsa-lecture.html](http://nobelprize.org/nobel_prizes/physics/laureates/1978/kapitsa-lecture.html)
- [10] [http://nobelprize.org/nobel\\_prizes/physics/laureates/1978/kapitsa-lecture.pdf](http://nobelprize.org/nobel_prizes/physics/laureates/1978/kapitsa-lecture.pdf) PLASMA AND THE CONTROLLED THERMONUCLEAR REACTION
- [11] [http://nobelprize.org/nobel\\_prizes/physics/laureates/1970/neel-lecture.html](http://nobelprize.org/nobel_prizes/physics/laureates/1970/neel-lecture.html) Louis Néel: "Magnetism and the Local Molecular Field"
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# Herbert S. Gutowsky

| Herbert S. Gutowsky                                                                                                                                               |                                                                                                                            |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|
| <br>Professor Herbert S. Gutowsky, Member of the US National Academy of Sciences |                                                                                                                            |
| <b>Born</b>                                                                                                                                                       | November 8, 1919<br>Bridgman, Michigan                                                                                     |
| <b>Died</b>                                                                                                                                                       | January 13, 2000<br>Urbana                                                                                                 |
| <b>Citizenship</b>                                                                                                                                                | USA                                                                                                                        |
| <b>Nationality</b>                                                                                                                                                | USA                                                                                                                        |
| <b>Ethnicity</b>                                                                                                                                                  | US                                                                                                                         |
| <b>Fields</b>                                                                                                                                                     | Nuclear magnetic resonance                                                                                                 |
| <b>Institutions</b>                                                                                                                                               | University of Illinois at Urbana                                                                                           |
| <b>Alma mater</b>                                                                                                                                                 | Harvard University                                                                                                         |
| <b>Doctoral advisor</b>                                                                                                                                           | George Kistiakowsky                                                                                                        |
| <b>Doctoral students</b>                                                                                                                                          | 35                                                                                                                         |
| <b>Known for</b>                                                                                                                                                  | Solid-state NMR and NMR spectroscopy                                                                                       |
| <b>Notable awards</b>                                                                                                                                             | Kistiakowsky prize, Wolf prize, Irving Langmuir prize, Peter Debye prize, Member of the National Academy of Sciences, USA. |

**Herbert S. Gutowsky** (November 8, 1919 - January 13, 2000) was an American chemist who was a Professor of Chemistry at the University of Illinois at Urbana-Champaign. His pioneering work made nuclear magnetic resonance spectroscopy one of the most effective tools in chemical and medical research.

## Birth and education

Herbert S. Gutowsky was born on November 8, 1919, on a produce farm in Bridgman, Michigan. He was the son of Otto and Hattie Neyer Gutowsky. He claimed that his childhood experiences taught him the importance of hard work, which carried over to his scientific life. He was a quiet, kind and thoughtful man who focused on science and who worked very closely with all his research associates. He was also an avid bicyclist in his early life, and also bird-watcher who later became very interested in growing roses in his own garden.

Gutowsky received a bachelor's degree from Indiana University in 1940, and after a four-year interruption for military service, he was awarded a master's degree from UC-Berkeley in 1946. Gutowsky earned his Ph.D. in chemistry from Harvard University under George Kistiakowsky.

## Academic career

He joined the faculty of the University of Illinois at Urbana-Champaign in 1948. He became a full professor in 1956. His research interests as a young faculty member included molecular and solid-state structure by infrared (IR) and radio frequency spectroscopy, including both nuclear magnetic resonance and electron paramagnetic resonance.

## Research on Nuclear Magnetic Resonance

Herbert S. Gutowsky was the first to apply the nuclear magnetic resonance method to chemical research. His experimental and theoretical work on the chemical shift effect and its relation to molecular structure has provided the chemist with working tools to study molecular conformation and molecular interactions in solutions. Gutowsky's pioneering work on the spin-spin coupling effect developed this phenomenon into a 'finger print' method for the identification and characterization of organic compounds. He was also the first to observe the effect of dynamic processes on the lineshape of high resolution nuclear magnetic resonance spectra, and exploited it for the studies of hindered rotation in molecules. Simultaneously with others he discovered the effect of the scalar and dipolar interaction with unpaired electrons in solutions of paramagnetic ions<sup>[1]</sup>.

He was awarded the Wolf Prize in Chemistry in 1983/84 for "his pioneering work in the development and applications of nuclear magnetic resonance spectroscopy in chemistry"<sup>[2]</sup>. More specifically, the latter prize committee cited explicitly his truly outstanding physical chemistry research results as follows: "*Professor Herbert S. Gutowsky was the first to apply the nuclear magnetic resonance method to chemical research. His experimental and theoretical work on the chemical shift effect and its relation to molecular structure has provided the chemist with working tools to study molecular conformation and molecular interactions in solutions. Gutowsky's pioneering work on the spin-spin coupling effect developed this phenomenon into a 'finger print' method for the identification and characterization of organic compounds. He was also the first to observe the effect of dynamic processes on the lineshape of high resolution nuclear magnetic resonance spectra, and exploited it for the studies of hindered rotation in molecules. Simultaneously with others he discovered the effect of the scalar and dipole-dipole interaction with unpaired electrons in solutions of paramagnetic ions.*"

## Later years

He became head of the Department of Chemistry at the University of Illinois at Urbana-Champaign in 1967, and in 1970 he oversaw the creation of the School of Chemical Sciences, which included the departments of chemistry and chemical engineering. He served as Director of the School of Chemical Sciences from 1970 to 1983.

During 1976--1986 he published in collaboration with a photosynthesis research group in the Biophysics Department the results of a series of NMR, fluorescence, pulsed light/oxygen evolution studies of biomembranes-- including photosynthetic plant membranes/thylakoids<sup>[3]</sup> <sup>[4]</sup> <sup>[5]</sup> and living, green algae<sup>[6]</sup> --investigating the complex physico-chemical mechanisms of photosynthesis involving  $\text{Mn}^{+2}$ ,  $\text{Mn}^{+3}$ ,  $\text{Cl}^-$  and  $\text{Br}^-$  ionic effects in photosynthetic oxygen evolution and photosynthetic water oxidation by photosystem II (PS-II) in the oxygen evolving complex (OEC)<sup>[7]</sup>.

After 1983 he focused on teaching and research, moving into a 'third research career' in Fourier-transform microwave spectroscopy studies of small, weakly bonded molecules in the gas phase. He died on January 13, 2000 in Urbana.

## Other Heads, Department of Chemistry, University of Illinois

| Head                | Years of Service | Years |
|---------------------|------------------|-------|
| A. P. S. Stewart    | 1868-1874        | 6     |
| Henry A. Weber      | 1874-1882        | 8     |
| William McMurtrie   | 1882-1888        | 6     |
| J. C. Jackson       | 1888             | 1     |
| Arthur W. Palmer    | 1889-1904        | 15    |
| Harry S. Grindley   | 1904-1907        | 3     |
| William A. Noyes    | 1907-1926        | 19    |
| Roger Adams         | 1926-1954        | 28    |
| Herbert E. Carter   | 1954-1967        | 13    |
| Herbert S. Gutowsky | 1967-1983        | 16    |
| Larry R. Faulkner   | 1984-1989        | 5     |
| Gary B. Schuster    | 1989-1994        | 5     |
| Paul W. Bohn        | 1995-1999        | 5     |
| Steven C. Zimmerman | 1999-2000        | 1     |
| Gregory S. Girolami | 2000-2005        | 5     |
| Steven C. Zimmerman | 2005-            |       |

### See also

- Charles Pence Slichter
- Nuclear magnetic resonance
- Chemical shift
- Knight shift
- Relaxation
- J-coupling
- Dynamic nuclear polarisation
- NMR spectroscopy
- Carbon-13 NMR
- Deuterium NMR
- 2D-FT NMRI and Spectroscopy
- Solid-state nuclear magnetic resonance
- NMR spectra database
- In vivo magnetic resonance spectroscopy

## External links

- Biography of Herbert S. Gutowsky <sup>[8]</sup>
- Herbert S. Gutowsky and NMR Spectroscopy <sup>[9]</sup>
- Nuclear Magnetic Resonance in Physical Chemistry <sup>[10]</sup>

## References

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  - [2] The Wolf Prize in Chemistry ([http://www.wolffund.org.il/cat.asp?id=15&cat\\_title=CHEMISTRY](http://www.wolffund.org.il/cat.asp?id=15&cat_title=CHEMISTRY))
  - [3] <http://www.pnas.org/cgi/content/abstract/81/12/3713?ck=nck>
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  - [7] <http://www.life.illinois.edu/govindjee/pubschron.html> C. Critchley, I.C. Baianu, Govindjee and H.S. Gutowsky(1982) The Role of Chloride in O<sub>2</sub> Evolution by Thylakoids from Salt-tolerant Higher Plants. *Biochim. Biophys. Acta* 682: 436-445.
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  - [9] <http://acswebcontent.acs.org/landmarks/landmarks/noyes/gutowsky.html>
  - [10] <http://planetphysics.org/?op=getobj&from=books&id=290>
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# Erwin Hahn

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| Erwin Hahn                                                                                                                                                                                   |                                      |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|
| <div><div>No free image</div><div></div><div>Do you own one?</div><div>If so, please click here</div></div> |                                      |
| <b>Born</b>                                                                                                                                                                                  | June 9, 1921<br>Sharon, Pennsylvania |
| <b>Fields</b>                                                                                                                                                                                | Physics                              |
| <b>Institutions</b>                                                                                                                                                                          | University of California, Berkeley   |

**Erwin L. Hahn** (born 1921) is a U.S. physicist, best known for his work on nuclear magnetic resonance (NMR).<sup>[1]</sup> In 1950 he discovered the spin echo.

He received his B.S. in Physics from Juniata College. He has been Professor Emeritus at the University of California, Berkeley since 1991 and was professor of physics, 1955-91.

## See also

- Pulsed magnetic resonance--NMR, ESR, and optics: a recognition of E.L. Hahn*. Oxford University Press. 1992. ISBN 0198539622.

## External links

- Oral History interview transcript with Erwin L. Hahn 21 August 1986, American Institute of Physics, Niels Bohr Library and Archives <sup>[2]</sup>

## References

[1] Filler, AG: The history, development, and impact of computed imaging in neurological diagnosis and neurosurgery: CT, MRI, DTI: Nature Precedings DOI: 10.1038/npre.2009.3267.4 (<http://precedings.nature.com/documents/3267/version/4>).

[2] <http://www.aip.org/history/ohilist/4652.html>

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# Peter Mansfield

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| Peter Mansfield                                                                   |                                              |
|-----------------------------------------------------------------------------------|----------------------------------------------|
|  |                                              |
| <b>Born</b>                                                                       | 9 October 1933                               |
| <b>Nationality</b>                                                                | British                                      |
| <b>Institutions</b>                                                               | University of Nottingham                     |
| <b>Known for</b>                                                                  | Magnetic Resonance Imaging                   |
| <b>Notable awards</b>                                                             | Nobel Prize in Physiology or Medicine (2003) |

**Sir Peter Mansfield**, FRS, (born 9 October 1933), is a British physicist who was awarded the 2003 Nobel Prize in Physiology or Medicine for his discoveries concerning magnetic resonance imaging (MRI). The Nobel Prize was shared with Paul Lauterbur, who also contributed to the development of MRI. Sir Peter is a professor at the University of Nottingham.

The Nobel Prize in Physics in 1952, which went to Felix Bloch and Edward Purcell, was for the development of nuclear magnetic resonance (NMR), the scientific principle behind MRI. For decades magnetic resonance was used mainly for studying the chemical structure of substances, and Mansfield's first project in this field was to develop a portable, transistorised Earth's field NMR (EFNMR) spectrometer in the late 1950s. It was not until the 1970s with Lauterbur's and Mansfield's developments that NMR could be used to produce images of the body. Mansfield is credited with showing how the radio signals from MRI can be mathematically analyzed, making interpretation of the signals into a useful image a possibility. He is also credited with discovering how fast imaging could be possible by developing the MRI protocol called echo-planar imaging. Echo-planar imaging allows T2\* weighted images to be collected many times faster than previously possible. It also has made functional magnetic resonance imaging (fMRI) feasible.

Mansfield came from humble beginnings in South East London, attending secondary school in Peckham. He left school at 15, and became a printer. He took A levels in night school. He then studied physics at Queen Mary College, London, graduating with a BSc in 1959 and a PhD in 1962.<sup>[1]</sup>

He has worked in the Department of Physics at the University of Nottingham since 1964.

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## External links

- University of Nottingham: Peter Mansfield homepage <sup>[2]</sup>
- Nobel Prize 2003 Press Release <sup>[3]</sup>
- Appearance <sup>[4]</sup> on Desert Island Discs
- Peter Mansfield US Patents <sup>[5]</sup>
- Peter Mansfield autobiography <sup>[6]</sup>

## References

- [1] "Queen Mary, University of London Notable Alumni and Staff" (<http://www.qmul.ac.uk/alumni/alumninetwork/notablealumni/index.html>). . Retrieved 2007-09-23.
- [2] <http://www.magres.nottingham.ac.uk/~mansfield/>
- [3] <http://nobelprize.org/medicine/laureates/2003/press.html>
- [4] [http://www.bbc.co.uk/radio4/factual/desertislanddiscs\\_20060618.shtml](http://www.bbc.co.uk/radio4/factual/desertislanddiscs_20060618.shtml)
- [5] <http://www.patentgenius.com/inventor/MansfieldPeter.html>
- [6] [http://nobelprize.org/nobel\\_prizes/medicine/laureates/2003/mansfield-autobio.html](http://nobelprize.org/nobel_prizes/medicine/laureates/2003/mansfield-autobio.html)
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# Paul Lauterbur

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| Paul Lauterbur                                                                    |                                                                                                                         |
|-----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|
|  |                                                                                                                         |
| <b>Born</b>                                                                       | May 6, 1929<br>Sidney, Ohio                                                                                             |
| <b>Died</b>                                                                       | March 27, 2007 (aged 77)                                                                                                |
| <b>Residence</b>                                                                  | United States                                                                                                           |
| <b>Institutions</b>                                                               | State University of New York at Stony Brook<br>University of Illinois at Urbana-Champaign<br>Carnegie Mellon University |
| <b>Alma mater</b>                                                                 | Case Western Reserve University<br>University of Pittsburgh                                                             |
| <b>Known for</b>                                                                  | Magnetic Resonance Imaging                                                                                              |
| <b>Notable awards</b>                                                             | Nobel Prize in Physiology or Medicine (2003)                                                                            |

**Paul Christian Lauterbur** (May 6, 1929 – March 27, 2007) was an American chemist who shared the Nobel Prize in Physiology or Medicine in 2003 with Peter Mansfield for his work which made the development of magnetic resonance imaging (MRI) possible.<sup>[1]</sup>

Dr. Lauterbur was a professor along with his wife Joan at the University of Illinois at Urbana-Champaign for 22 years until his death in Urbana. He never stopped working with undergraduates on research, and he served as a professor of chemistry, with appointments in bioengineering, biophysics and computational biology at the Center for Advanced Study.<sup>[2]</sup>

## Early life

Born and raised in Sidney, Ohio, Lauterbur graduated from Sidney High School, where a new Chemistry, Physics, and Biology wing was dedicated in his honor. He did his undergraduate work at Case Institute of Technology in Cleveland, which is now known as Case Western Reserve University. As a teenager, he built his own laboratory in the basement of his parents' house.<sup>[3]</sup> His chemistry teacher at school understood that he enjoyed experimenting on his own, so the teacher allowed him to do his own experiments at the back of class.<sup>[3]</sup> When he was drafted into the Army in the 1950s, his superiors allowed him to spend his time working on an early nuclear magnetic resonance (NMR) machine; he had published four scientific papers by the time he left the Army.<sup>[3]</sup>

## The development of the MRI

Lauterbur is a 1962 graduate of the University of Pittsburgh and credits the idea of the MRI to a brainstorm one day at a suburban Pittsburgh Big Boy, with the MRI's first model scribbled on a table napkin.<sup>[4]</sup> <sup>[3]</sup> The further research that led to the Nobel Prize was performed at Stony Brook University<sup>[5]</sup> in the 1970s.

The Nobel Prize in Physics in 1952, which went to Felix Bloch and Edward Purcell, was for the development of nuclear magnetic resonance (NMR), the scientific principle behind MRI. However, for decades magnetic resonance was used mainly for studying the chemical structure of substances. It wasn't until the 1970s with Lauterbur's and Mansfield's developments that NMR could be used to produce images of the body.

Lauterbur is credited for the idea of introducing gradients in the magnetic field which allows for determining the origin of the radio waves emitted from the nuclei of the object of study. This spatial information allows two-dimensional pictures to be produced.<sup>[3]</sup>

While Lauterbur conducted his work at Stony Brook, the best NMR machine on campus belonged to the chemistry department; he would have to visit it at night to use it for experimentation and would carefully change the settings so that they would return to those of the chemists' as he left.<sup>[6]</sup> A replica of his original MRI machine is located at the Chemistry building on the campus of the State University of New York at Stony Brook in Stony Brook, New York.

Some of the first images taken by Lauterbur included those of a clam his daughter had collected on the beach at the Long Island Sound, green peppers<sup>[3]</sup> and two test tubes of heavy water within a beaker of ordinary water; no other imaging technique in existence at that time could distinguish between two different kinds of water. The human body consists mostly of water.<sup>[6]</sup>

When Lauterbur first submitted his paper with his discoveries to *Nature*, the paper was rejected by the editors of the journal. Lauterbur persisted and requested them to review it again, upon which time it was published and is now acknowledged as a classic *Nature* paper.<sup>[7]</sup> The *Nature* editors pointed out that the pictures accompanying the paper were too fuzzy, although they were the first images to show the difference between heavy water and ordinary water.<sup>[3]</sup> Lauterbur said of the initial rejection: "You could write the entire history of science in the last 50 years in terms of papers rejected by *Science* or *Nature*."<sup>[6]</sup>

Peter Mansfield of the University of Nottingham in the United Kingdom took Lauterbur's initial work another step further, developing a mathematical process to speed the image reading.<sup>[6]</sup>

Lauterbur attempted to file patents related to his work to commercialize it unsuccessfully.<sup>[8]</sup> Stony Brook chose not to pursue patents, thinking that the expense would not pay off in the end. "The company that was in charge of such applications decided that it would not repay the expense of getting a patent. That turned out not to be a spectacularly good decision," Lauterbur said in 2003. He attempted to get the federal government to pay for an early prototype of the MRI machine for years in the 1970s, and the process took a decade.<sup>[9]</sup> The University of Nottingham did file patents which later made Mansfield wealthy.<sup>[9]</sup>

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## Nobel Prize

Lauterbur was awarded the Nobel Prize along with Mansfield in the fall of 2003. Controversy occurred when Raymond Damadian took out full-page ads in *The New York Times*, *The Washington Post* and *The Los Angeles Times* headlined "The Shameful Wrong That Must Be Righted" saying that the Nobel committee had not included him as a Prize winner alongside Lauterbur and Mansfield for his early work on the MRI. Damadian claimed that he discovered MRI and the two Nobel-winning scientists refined his technology. *The New York Times* published an editorial saying that while scientists credit Damadian for holding an early patent in MRI technology, Lauterbur and Mansfield conducted the work that led

to present MRI technology. The newspaper pointed out a few cases in which precursor discoveries had been awarded with a Nobel, along with a few deserving cases in which it had not, such as Rosalind Franklin and Oswald Avery.<sup>[10]</sup>  
[11]



U.S. President George W. Bush with the six 2003 American Nobel laureates in the Oval Office. From left to right, Dr. Roderick MacKinnon, New York City (chemistry); Dr. Anthony Leggett, Urbana, Illinois (physics); Dr. Robert Engle, New York City (economics); Dr. Alexei Abrikosov, Argonne, Illinois (physics); Dr. Peter Agre, Baltimore, Maryland (chemistry); and Dr. Paul Lauterbur, Urbana, Illinois (physiology/medicine).

## Death

Lauterbur died in March 2007 of kidney disease at his home in Urbana, Illinois. University of Illinois Chancellor Richard Herman said, "Paul's influence is felt around the world every day, every time an MRI saves the life of a daughter or a son, a mother or a father."<sup>[11]</sup>

## Other awards and honors

- Albert Lasker Award for Clinical Medical Research, 1984
- General Motors Cancer Research Foundation Kettering Prize, 1985
- National Medal of Science, 1987
- National Medal of Technology, 1988, (with Raymond Damadian)<sup>[8]</sup>
- Bower Award, Franklin Institute of Philadelphia, 1990 (first recipient)
- Carnegie Mellon Dickson Prize in Science in 1993.<sup>[2]</sup>
- Charter member, Phi Kappa Tau Hall of Fame in 2006.
- National Inventors Hall of Fame, class of 2007

Honorary Degrees:

- Carnegie-Mellon University in Pittsburgh
- University of Liège in Belgium
- Nicolaus Copernicus University Medical School in Kraków, Poland

## See also

- Nobel Prize controversies

## External links

- Nobel Prize 2003 Press Release <sup>[3]</sup>
- University of Pittsburgh Medical School article on alumnus Lauterbur <sup>[12]</sup>
- Paul C. Lauterbur Patents <sup>[13]</sup>
- Paul Lauterbur <sup>[14]</sup> at Find a Grave
- [15] Article on MRI

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- [1] Filler, AG: The history, development, and impact of computed imaging in neurological diagnosis and neurosurgery: CT, MRI, DTI: Nature Precedings DOI: 10.1038/npre.2009.3267.4 (<http://precedings.nature.com/documents/3267/version/4>).
- [2] Spice, Byron (2003-10-07). "Nobel Prize for MRI began with a burger in New Kensington" (<http://www.post-gazette.com/pg/03280/228666.stm>). *Pittsburgh Post-Gazette*. . Retrieved 2007-08-05.
- [3] "Paul Lauterbur" ([http://www.economist.com/obituary/displaystory.cfm?story\\_id=8954439](http://www.economist.com/obituary/displaystory.cfm?story_id=8954439)). *The Economist*. 2007-04-07. . Retrieved 2007-08-04.
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- [14] <http://www.findagrave.com/cgi-bin/fg.cgi?page=gr&GRid=18681702>
- [15] <http://www.vigyanprasar.gov.in/comcom/feature69.htm>

# Alberte Pullman

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**Alberte Pullman** (née Bucher) was born in France in 1920. She is a theoretical and quantum chemist. She studied at the Sorbonne starting in 1938. During her studies she worked on calculations at Centre National de la Recherche Scientifique (CNRS). From 1943 she worked with Raymond Daudel. She completed her doctorate in 1946. On his return from war service in 1946, she married Bernard Pullman. She and her husband worked together until his death in 1996. Together they wrote several books including *Quantum Biochemistry*, Interscience Publishers, 1963. Their work in the 1950s and 1960s was the beginning of the new field of Quantum Biochemistry. They pioneered the application of quantum chemistry to predicting the carcinogenic properties of aromatic hydrocarbons.



She is a member of the International Academy of Quantum Molecular Science and a member and former President of The International Society of Quantum Biology and Pharmacology.<sup>[1]</sup>

## External links

- An interview with Mme Prof. Dr. Alberte Pullman <sup>[2]</sup>

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# Bernard Pullman

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**Bernard Pullman** (March 19, 1919, Wloclawek Poland -- 1996) was a French theoretical quantum chemist and quantum biochemist.

Pullman studied at the Sorbonne, then spent the Second World War as a French Army officer in Africa and the Middle East. Returning to Paris in 1946, he completed the Licence-es-Sciences in 1946 and the Docteur-es-Science in 1948. From 1946 to 1954, he worked at the Centre National de la Recherche Scientifique (CNRS). In 1954 he was appointed Professor at the Sorbonne. In 1959, he became Director of the Department of Quantum Biochemistry at the Institut de Biologie Physico-Chimique. In 1963, he was promoted to Director of the Institute. He was a founding member of the International Academy of Quantum Molecular Science.

Over the course of his career, Pullman published about 400 scientific papers and 5 books, three with his wife Alberte Pullman, his lifelong collaborator. In joint work published in the 1950s and 1960s, they founded the new field of quantum biochemistry. They also pioneered the application of quantum chemistry to predicting the carcinogenic properties of aromatic hydrocarbons.

After his 1989 retirement, he wrote *The Atom in the History of Human Thought* (Paris: Fayard, 1995), a work approachable by general readers.

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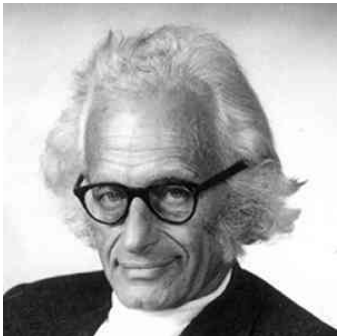
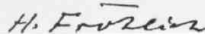
## External links

- His International Academy of Quantum Molecular Science page <sup>[1]</sup>
- An interview with Mme Prof. Dr. Alberte Pullman <sup>[2]</sup>

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# Herbert Fröhlich

| Herbert Fröhlich                                                                                                      |                                                                                                                                                                   |
|-----------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  <p>Herbert Fröhlich (1905-1991)</p> |                                                                                                                                                                   |
| <b>Born</b>                                                                                                           | 9 December 1905<br>Rexingen, Germany                                                                                                                              |
| <b>Died</b>                                                                                                           | 23 January 1991 (aged 86)<br>Liverpool, England                                                                                                                   |
| <b>Residence</b>                                                                                                      | UK                                                                                                                                                                |
| <b>Nationality</b>                                                                                                    | British                                                                                                                                                           |
| <b>Ethnicity</b>                                                                                                      | Jewish-German                                                                                                                                                     |
| <b>Fields</b>                                                                                                         | Physicist                                                                                                                                                         |
| <b>Institutions</b>                                                                                                   | University of Bristol<br>University of Liverpool<br>University of Salford<br>Ioffe Physico-Technical Institute<br>University of Freiburg<br>University of Bristol |
| <b>Alma mater</b>                                                                                                     | Ludwig-Maximilians University                                                                                                                                     |
| <b>Doctoral advisor</b>                                                                                               | Arnold Sommerfeld                                                                                                                                                 |
| <b>Doctoral students</b>                                                                                              | Sebastian Doniach<br>Gerard Hyland                                                                                                                                |
| <b>Other notable students</b>                                                                                         | Sigurd Zienau                                                                                                                                                     |
| <b>Known for</b>                                                                                                      | Fröhlich coherence<br>Fröhlich polaron<br>Fröhlich Hamiltonian<br>Fröhlich term                                                                                   |
| <b>Notable awards</b>                                                                                                 | Max-Planck Medal (1972)                                                                                                                                           |
| <p><b>Signature</b></p>            |                                                                                                                                                                   |
| <b>Notes</b>                                                                                                          | He is the brother of the mathematician Albrecht Fröhlich.                                                                                                         |

**Herbert Fröhlich** (9 December 1905 in Rexingen, Germany – 23 January 1991 in Liverpool, England) was a German-born British physicist and a Fellow of the Royal Society.

Fröhlich was the son of Fanny Frida (née Schwarz) and Jakob Julius Fröhlich, members of an old-established Jewish family.

## Career

In 1927, Fröhlich entered the Ludwig-Maximilians University, Munich, to study physics, and he received his doctorate under Arnold Sommerfeld, in 1930.<sup>[1]</sup> His first position was as Privatdozent at the University of Freiburg. Due to rising anti-Semitism and the Deutsche Physik movement under Adolf Hitler, and at the invitation of Yakov Frenkel, Fröhlich went to the Soviet Union, in 1933, to work at the Ioffe Physico-Technical Institute in Leningrad. During the Great Purge following the murder of Sergey Kirov, he fled to England in 1935. Except for a short visit to Holland and a brief internment during World War II, he worked in Nevill Francis Mott's department, at the University of Bristol, until 1948, rising to the position of Reader. At the invitation of James Chadwick, he took the Chair for Theoretical Physics at the University of Liverpool.

He was offered by the Bell Telephone Laboratories a handsome salary to go to Princeton University as their specially endowed professor. But at Liverpool he had a purely research post, which was attractive to him, and he was newly married to an American postgraduate philosophy student, and later an artist, Fanchon Aungst, who was not keen to return to America at that time.

From 1973, he was Professor of Solid State Physics at the University of Salford, however, all the while maintaining an office at the University of Liverpool, where he gained emeritus status in 1976 until his death. During 1981, he was a visiting professor at Purdue University.<sup>[2] [3] [4]</sup>

Fröhlich proposed a theory which is known as Fröhlich coherence.<sup>[5] [6]</sup>

## Honours

- 1951 – Fellow of the Royal Society
- 1972 – Deutsche Physikalische Gesellschaft Max-Planck Medal

## Books

- Herbert Fröhlich *Elektronentheorie der Metalle. (Struktur und Eigenschaften der Materie in Eigendarstellung, Bd.18)*. (Springer, 1936, 1969)
  - Herbert Fröhlich *Elektronentheorie der Metalle* (Ann Arbor: Edwards Brothers, First US edition, in German, 1943) ISBN 1114566489
  - Herbert Fröhlich *Theory of Dielectrics: Dielectric Constant and Dielectric Loss* (Clarendon Press, 1949, 1958)
  - Herbert Fröhlich and F. Kremer *Coherent Excitations in Biological Systems* (Springer-Verlag, 1983)
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- Terence W. Barrett and Herbert A. Pohl *Energy Transfer Dynamics: Studies and Essays in Honor of Herbert Frohlich on His Eightieth Birthday* (Springer-Verlag, 1987) ISBN 978-3540175025
- GJ Hyland and Peter Rowlands (editors) *Herbert Frohlich FRS: A Physicist Ahead of his Time*. (University of Liverpool, 2006, 2nd edition 2008.) ISBN 978-0-906370-57-5

## See also

- Quantum mind

## External links

- Fröhlich Biography <sup>[7]</sup> – International Institute of Biophysics
- NCUACS Fröhlich archive <sup>[8]</sup>
- Liverpool Univ bio <sup>[9]</sup>
- Fröhlich's math genealogy <sup>[10]</sup>

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# Notable mathematicians with interests in Biology

## Alexander Grothendieck

| Alexander Grothendieck                                                                                                                             |                                                                  |
|----------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------|
| <div>  </div> <div>Alexander Grothendieck in Montreal, 1970</div> |                                                                  |
| <b>Born</b>                                                                                                                                        | 28 March 1928<br>Berlin, Germany                                 |
| <b>Residence</b>                                                                                                                                   | France                                                           |
| <b>Fields</b>                                                                                                                                      | algebraic geometry, homological algebra, and functional analysis |
| <b>Alma mater</b>                                                                                                                                  | University of Montpellier, University of Nancy                   |
| <b>Doctoral advisor</b>                                                                                                                            | Laurent Schwartz                                                 |
| <b>Doctoral students</b>                                                                                                                           | Pierre Deligne, Jean-Louis Verdier, Michel Raynaud               |
| <b>Notable awards</b>                                                                                                                              | Fields Medal (1966), Crafoord Prize(1988, declined)              |

**Alexander Grothendieck** (born March 28, 1928 in Berlin, Germany) is one of the most influential mathematicians of the twentieth century, known principally for his revolutionary advances in algebraic geometry, but also for major contributions to algebraic topology, number theory, category theory, Galois theory, descent theory, commutative homological algebra and functional analysis. He was awarded the Fields Medal in 1966, and was co-awarded the Crafoord Prize with Pierre Deligne in 1988, but Grothendieck declined it.

He is noted for his mastery of abstract approaches to mathematics, and his perfectionism in matters of formulation and presentation. In particular, he demonstrated the ability to derive concrete results using only very general methods. Relatively little of his work after 1960 was published by the conventional route of the learned journal, circulating initially in duplicated volumes of seminar notes; his influence was to a considerable extent personal, on French mathematics and the Zariski school at Harvard University. He retired in 1988 and within a few years became reclusive.

## Mathematical achievements

Grothendieck's early mathematical work was done in functional analysis between 1949 and 1953 working on (what became) his doctoral thesis in Nancy, supervised by Jean Dieudonné and Laurent Schwartz. His key contributions include topological tensor products of vector spaces, the theory of nuclear spaces and the application of  $L^p$  spaces in studying linear maps between topological vector spaces. In the space of a few years, he had turned himself into a leading authority on the theory of topological vector spaces — to the extent that Dieudonné compares his impact in this field to that of Banach.<sup>[1]</sup>

However, it is algebraic geometry and related fields where Grothendieck did his most important and influential work. From about 1955 he started to work on sheaf theory and homological algebra, rapidly producing the very influential "Tôhoku paper" (*Sur quelques points d'algèbre homologique*, published in 1957) where he introduced Abelian categories and applied it to show that sheaf cohomology can be defined as certain derived functors in this context.

Homological methods and sheaf theory had already been introduced in algebraic geometry by Jean-Pierre Serre and others, after sheaves had been defined by Jean Leray. Grothendieck took them to a higher level of abstraction and turned them into a key organising principle of his theory. He thereby changed the tools and the level of abstraction in algebraic geometry. He shifted attention from the study of individual varieties to the *relative point of view* (pairs of varieties related by a morphism), allowing a broad generalization of many classical theorems. The first major application was the relative version of Serre's theorem showing that the cohomology of a coherent sheaf on a complete variety is finite dimensional; Grothendieck's theorem shows that the higher direct images of coherent sheaves under a proper map are coherent; this reduces to Serre's theorem over a one-point space.

Next, in 1956, he applied the same thinking to the Riemann–Roch theorem, which had already recently been generalized to any dimension by Hirzebruch. The Grothendieck–Riemann–Roch theorem was announced by Grothendieck at the initial Mathematische Arbeitstagung in Bonn, in 1957. It appeared in print in a paper written by Armand Borel with Serre. This result was his first major achievement in algebraic geometry. He went on to plan and execute a major foundational programme for rebuilding the foundations of algebraic geometry; he exposed the main outlines of this programme in his talk at the 1958 International Congress of Mathematicians.

His foundational work on algebraic geometry is at a higher level of abstraction than all prior versions. He adapted the use of non-closed generic points, which led to the theory of schemes. He also pioneered the systematic use of nilpotents. As 'functions' these can take only the value 0, but they carry infinitesimal information, in purely algebraic settings. His *theory of schemes* has become established as the best universal foundation for this major field, because of its great expressive power as well as technical depth. In that setting one can use birational geometry, techniques from number theory, Galois theory and commutative algebra, and close analogues of the methods of algebraic topology, all in an integrated way.<sup>[2] [3] [4]</sup>

His influence spilled over into many other branches of mathematics, for example the contemporary theory of D-modules. (It also provoked adverse reactions, with many mathematicians seeking out more concrete areas and problems.)<sup>[5] [6]</sup>

## EGA and SGA

The bulk of Grothendieck's published work is collected in the monumental, and yet incomplete, *Éléments de géométrie algébrique* (EGA) and *Séminaire de géométrie algébrique* (SGA). The collection *Fondements de la Géométrie Algébrique* (FGA), which gathers together talks given in the Séminaire Bourbaki, also contains important material.

Perhaps Grothendieck's deepest single accomplishment is the invention of the étale and l-adic cohomology theories, which explain an observation of André Weil's that there is a deep connection between the topological characteristics of a variety and its diophantine (number theoretic) properties. For example, the number of solutions of an equation over a finite field reflects the topological nature of its solutions over the complex numbers. Weil realized that to prove such a connection one needed a new cohomology theory, but neither he nor any other expert saw how to do this until such a theory was found by Grothendieck.

This program culminated in the proofs of the Weil conjectures, the last of which was settled by Grothendieck's student Pierre Deligne in the early 1970s after Grothendieck had largely withdrawn from mathematics.

## Major mathematical topics (from *Récoltes et Semailles*)

He wrote a retrospective assessment of his mathematical work (see the external link *La Vision* below). As his main mathematical achievements ("maître-thèmes"), he chose this collection of 12 topics (his chronological order):

1. Topological tensor products and nuclear spaces
2. "Continuous" and "discrete" duality (derived categories and "six operations").
3. *Yoga* of the Grothendieck–Riemann–Roch theorem (K-theory, relation with intersection theory).
4. Schemes.
5. Topoi.
6. Étale cohomology including l-adic cohomology.
7. Motives and the motivic Galois group (and Grothendieck categories)
8. Crystals and crystalline cohomology, *yoga* of De Rham and Hodge coefficients.
9. Topological algebra, infinity-stacks, 'dérivateurs', cohomological formalism of toposes as an inspiration for a new homotopic algebra
10. Tame topology.
11. *Yoga* of anabelian geometry and Galois–Teichmüller theory.
12. Schematic point of view, or "arithmetics" for regular polyhedra and regular configurations of all sorts.

He wrote that the central theme of the topics above is that of topos theory, while the first and last were of the least importance to him.

Here the term *yoga* denotes a kind of "meta-theory" that can be used heuristically. The word *yoke*, meaning "linkage", is derived from the same Indo-European root.

## Life

### Family and early life

Alexander Grothendieck was born in Berlin to anarchist parents: a Russian father from an ultimately Hassidic family, Alexander "Sascha" Shapiro aka Tanaroff, and a mother from a German Protestant family, Johanna "Hanka" Grothendieck; both of his parents had broken away from their early backgrounds in their teens.<sup>[7]</sup> At the time of his birth Grothendieck's mother was married to Johannes Raddatz, a German journalist, and his birthname was initially recorded as *Alexander Raddatz*. The marriage was dissolved in 1929 and Shapiro/Tanaroff acknowledged his paternity, but never married Hanka Grothendieck.<sup>[7]</sup> Grothendieck lived with his parents until 1933 in Berlin. At the end of that year, Shapiro moved to Paris, and Hanka followed him the next year. They left Grothendieck in the care

of Wilhelm Heydorn, a Lutheran Pastor and teacher<sup>[8]</sup> in Hamburg where he went to school. During this time, his parents fought in the Spanish Civil War.

## **During WWII**

In 1939 Grothendieck came to France and lived in various camps for displaced persons with his mother, first at the Camp de Rieucros, and subsequently lived for the remainder of the war in the village of Le Chambon-sur-Lignon, where he, along with other Jewish children, was sheltered and hidden in local boarding-houses or pensions. His father was sent via Drancy to Auschwitz where he died in 1942. While Grothendieck lived in Chambon, he attended the Collège Cévenol (now known as the Le Collège-Lycée Cévenol International), a unique secondary school founded in 1938 by local Protestant pacifists and anti-war activists. Many of the other Jewish refugee children being hidden in Chambon attended Cévenol and it was at this school that Grothendieck apparently first became fascinated with mathematics.

## **Studies and contact with research mathematics**

After the war, the young Grothendieck studied mathematics in France, initially at the University of Montpellier. He had decided to become a math teacher because he had been told that mathematical research had been completed early in the 20th century and there were no more open problems.<sup>[9]</sup> However, his talent was noticed, and he was encouraged to go to Paris in 1948.

Initially, Grothendieck attended Henri Cartan's Seminar at École Normale Supérieure, but lacking the necessary background to follow the high-powered seminar, he moved to the University of Nancy where he wrote his dissertation under Laurent Schwartz in functional analysis, from 1950 to 1953. At this time he was a leading expert in the theory of topological vector spaces. By 1957, he set this subject aside in order to work in algebraic geometry and homological algebra.

## **The IHÉS years**

Installed at the Institut des Hautes Études Scientifiques (IHÉS), Grothendieck attracted attention by an intense and highly productive activity of seminars (*de facto* working groups drafting into foundational work some of the ablest French and other mathematicians of the younger generation). Grothendieck himself practically ceased publication of papers through the conventional, learned journal route. He was, however, able to play a dominant role in mathematics for around a decade, gathering a strong school.

During this time he had officially as students Michel Demazure (who worked on SGA3, on group schemes), Luc Illusie (cotangent complex), Michel Raynaud, Jean-Louis Verdier (cofounder of the derived category theory) and Pierre Deligne. Collaborators on the SGA projects also included Mike Artin (étale cohomology) and Nick Katz (monodromy theory and Lefschetz pencils). Jean Giraud worked out torsor theory extensions of non-abelian cohomology. Many others were involved.

## **The 'Golden Age'**

Alexander Grothendieck's work during the 'Golden Age' period at IHÉS established several unifying themes in algebraic geometry, number theory, topology, category theory and complex analysis. His first (pre-IHÉS) breakthrough in algebraic geometry was the Grothendieck–Hirzebruch–Riemann–Roch theorem, a far-reaching generalisation of the Hirzebruch–Riemann–Roch theorem proved algebraically; in this context he also introduced K-theory. Then, following the programme he outlined in his talk at the 1958 International Congress of Mathematicians, he introduced the theory of schemes, developing it in detail in his *Éléments de géométrie algébrique* (EGA) and providing the new more flexible and general foundations for algebraic geometry that has been adopted in the field since that time. He went on to introduce the étale cohomology theory of schemes, providing the key tools for proving the Weil conjectures, as well as crystalline cohomology and algebraic de Rham cohomology to



complement it. Closely linked to these cohomology theories, he originated topos theory as a generalisation of topology (relevant also in mathematical logic, category theory, and also to computer software programming and institutional ontology classification and bioinformatics). He also provided an algebraic definition of fundamental groups of schemes and more generally the main structures of a categorical Galois theory. As a framework for his coherent duality theory he also introduced derived categories, which were further developed by Verdier.

The results of work on these and other topics were published in the EGA and in less polished form in the notes of the Séminaire de géométrie algébrique (SGA) that he directed at IHES.

### Politics and retreat from scientific community

Grothendieck's political views were radical and pacifist. Thus he strongly opposed both United States aggression in Vietnam as well as Soviet military expansionism. He gave lectures on category theory in the forests surrounding Hanoi while the city was being bombed, to protest against the Vietnam War (*The Life and Work of Alexander Grothendieck*, American Math. Monthly, vol. 113, no. 9, footnote 6). He retired from scientific life around 1970, after having discovered the partly military funding of IHÉS (see pp. xii and xiii of SGA1, Springer Lecture Notes 224). He returned to academia a few years later as a professor at the University of Montpellier, where he stayed until his retirement in 1988. His criticisms of the scientific community, and especially of several mathematics circles, are also contained in a letter, written in 1988, in which he states the reasons for his refusal of the Crafoord Prize.<sup>[10]</sup> He declined the prize on ethical grounds in an open letter to the media.<sup>[11]</sup>

While the issue of military funding was perhaps the most obvious explanation for Grothendieck's departure from IHÉS, those who knew him say that the causes of the rupture ran deeper. Pierre Cartier, a *visiteur de longue durée* ("long-term guest") at the IHÉS, wrote a piece about Grothendieck for a special volume published on the occasion of the IHÉS's fortieth anniversary. The *Grothendieck Festschrift* was a three-volume collection of research papers to mark his sixtieth birthday (falling in 1988), and published in 1990.<sup>[12]</sup>

In it Cartier notes that, as the son of an antimilitary anarchist and one who grew up among the disenfranchised, Grothendieck always had a deep compassion for the poor and the downtrodden. As Cartier puts it, Grothendieck came to find Bures-sur-Yvette "*une cage dorée*" ("a golden cage"). While Grothendieck was at the IHÉS, opposition to the Vietnam War was heating up, and Cartier suggests that this also reinforced Grothendieck's distaste at having become a mandarin of the scientific world. In addition, after several years at the IHÉS Grothendieck seemed to cast about for new intellectual interests. By the late 1960s he had started to become interested in scientific areas outside of mathematics. David Ruelle, a physicist who joined the IHÉS faculty in 1964, said that Grothendieck came to talk to him a few times about physics. (In the 1970s Ruelle and the Dutch mathematician Floris Takens produced a new model for turbulence, and it was Ruelle who invented the concept of a strange attractor in a dynamical system.) Biology interested Grothendieck much more than physics, and he organized some seminars on biological topics.<sup>[13]</sup>

After leaving the IHÉS, Grothendieck tried but failed to get a position at the Collège de France.

He then went to Université de Montpellier, where he became increasingly estranged from the mathematical community. Around this time, he founded a group called *Survivre*, which was dedicated to antimilitary and ecological issues. His mathematical career, for the most part, ended when he left the IHÉS. In 1984 he wrote a proposal to get a position through the Centre National de la Recherche Scientifique. The proposal, entitled *Esquisse d'un Programme* ("Program Sketch") describes new ideas for studying the moduli space of complex curves. Although Grothendieck himself never published his work in this area, the proposal became the inspiration for work by other mathematicians and the source of the theory of dessin d'enfants. *Esquisse d'un Programme* was published in the two-volume proceedings *Geometric Galois Actions* (Cambridge University Press, 1997).<sup>[14]</sup>

## Manuscripts written in the 1980s

While not publishing mathematical research in conventional ways during the 1980s, he produced several influential manuscripts with limited distribution, with both mathematical and biographical content. During that period he also released his work on Bertini type theorems contained in EGA 5, published by the Grothendieck Circle <sup>[15]</sup> in 2004.

*La Longue Marche à travers la théorie de Galois* [*The Long March Through Galois Theory*] is an approximately 1600-page handwritten manuscript produced by Grothendieck during the years 1980–1981, containing many of the ideas leading to the *Esquisse d'un programme* <sup>[16]</sup> (see below, and also a more detailed entry), and in particular studying the Teichmüller theory. (For an English translation of the tables of contents of these manuscripts see the Wikipedia separate entry on the *Esquisse d'un programme*.)

In 1983 he wrote a huge extended manuscript (about 600 pages) entitled *Pursuing Stacks*, stimulated by correspondence with Ronald Brown, (see also R.Brown <sup>[17]</sup> and Tim Porter at University of Bangor in Wales), and starting with a letter addressed to Daniel Quillen. This letter and successive parts were distributed from Bangor (see External Links below): in an informal manner, as a kind of diary, Grothendieck explained and developed his ideas on the relationship between algebraic homotopy theory and algebraic geometry and prospects for a noncommutative theory of stacks. The manuscript, which is being edited for publication by G. Maltsiniotis, later led to another of his monumental works, *Les Dérivateurs*. Written in 1991, this latter opus of about 2000 pages further developed the homotopical ideas begun in *Pursuing Stacks*. Much of this work anticipated the subsequent development of the motivic homotopy theory of F. Morel and V. Voevodsky in the mid 1990s.

His *Esquisse d'un programme* <sup>[16]</sup> (1984) is a proposal for a position at the Centre National de la Recherche Scientifique, which he held from 1984 to his retirement in 1988. Ideas from it have proved influential, and have been developed by others, in particular dessins d'enfants and a new field emerging as anabelian geometry. In *La Clef des Songes* he explains how the reality of dreams convinced him of God's existence.

The 1000-page autobiographical manuscript *Récoltes et semailles* (1986) is now available on the internet in the French original, and an English translation is underway (these parts of *Récoltes et semailles* have already been translated into Russian] and published in Moscow <sup>[18]</sup>). Some parts of *Récoltes et semailles* <sup>[19]</sup> <sup>[20]</sup> and the whole *La Clef des Songes* <sup>[21]</sup> have been translated into Spanish.

## Retirement into reclusion

In 1991, Grothendieck moved to an address he did not provide to his previous contacts in the mathematical community. He is now said to live in southern France or Andorra and to be reclusive.

## See also

- Ax-Grothendieck theorem
- Birkhoff–Grothendieck theorem
- Esquisse d'un Programme
- Grothendieck category <sup>[22]</sup>
- Grothendieck's connectedness theorem
- Grothendieck connection
- Grothendieck construction
- Grothendieck's Galois theory
- Grothendieck group
- Grothendieck inequality or Grothendieck constant
- Grothendieck–Katz p-curvature conjecture
- Grothendieck's relative point of view
- Grothendieck–Riemann–Roch theorem

- Grothendieck's Séminaire de géométrie algébrique
- Grothendieck space
- Grothendieck spectral sequence
- Grothendieck topology
- Grothendieck universe
- Tarski–Grothendieck set theory
- IHES
- IHES at Forty by Allyn Jackson <sup>[23]</sup>

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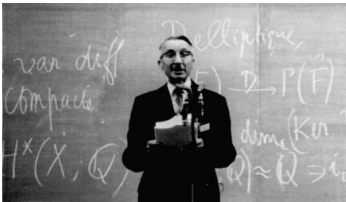
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- Alexander Grothendieck <sup>[35]</sup> at the Mathematics Genealogy Project
- Grothendieck Circle <sup>[36]</sup>, collection of mathematical and biographical information, photos, links to his writings
- Institut des Hautes Études Scientifiques <sup>[37]</sup>
- The origins of 'Pursuing Stacks' <sup>[38]</sup> This is an account of how 'Pursuing Stacks' was written in response to a correspondence in English with Ronnie Brown and Tim Porter <sup>[39]</sup> at Bangor, which continued until 1991.
- Récoltes et Semailles <sup>[40]</sup> in French.
- Spanish translation <sup>[41]</sup> of "Récoltes et Semailles" et "Le Clef des Songes" and other Grothendieck's texts
- short bio <sup>[31]</sup> from Notices of the American Mathematical Society

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# Henri Cartan

| Henri Cartan                                                                      |                                                |
|-----------------------------------------------------------------------------------|------------------------------------------------|
|  |                                                |
| Born                                                                              | July 8, 1904<br>Nancy, France                  |
| Died                                                                              | August 13, 2008<br>(aged 104)<br>Paris, France |
| Nationality                                                                       | French                                         |
| Occupation                                                                        | Mathematician                                  |
| Spouse(s)                                                                         | Nicole Antoinette Weiss                        |
| Parents                                                                           | Élie Cartan<br>Marie-Louise Bianconi           |

| Henri Cartan      |                                                                                                                                                                                                                                                                 |
|-------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Fields            | Algebraic<br>topology<br>Bourbaki                                                                                                                                                                                                                               |
| Doctoral advisor  | Paul Montel                                                                                                                                                                                                                                                     |
| Doctoral students | Jean-Paul<br>Benzécri<br>Jean-Paul<br>Brasselet<br>Pierre Cartier<br>Jean Cerf<br>Jacques Deny<br>Adrien Douady<br>Roger Godement<br>Max Karoubi<br>Jean-Louis Koszul<br>Joshua Leslie<br>Jean-Pierre Ramis<br>Jean-Pierre Serre<br>Banwari Sharma<br>René Thom |

**Henri Paul Cartan** (July 8, 1904 – August 13, 2008) was a son of Élie Cartan, and was, as his father was, a distinguished and influential French mathematician.<sup>[1]</sup>

## Life

Cartan studied at the Lycée Hoche in Versailles, then at the ENS, receiving his doctorate in mathematics. He taught at the University of Strasbourg from November 1931 until the outbreak of the Second World War, after which he held academic positions at a number of other French universities, spending the bulk of his working life in Paris.

Cartan was known for work in algebraic topology, in particular on cohomology operations, Killing homotopy groups and group cohomology. His seminar in Paris in the years after 1945 covered ground on several complex variables, sheaf theory, spectral sequences and homological algebra, in a way that deeply influenced Jean-Pierre Serre, Armand Borel, Alexander Grothendieck and Frank Adams, amongst others of the leading lights of the younger generation. The number of his official students was small, but includes Adrien Douady, Roger Godement, Max Karoubi, Jean-Pierre Serre and René Thom.

Cartan also was a founding member of the Bourbaki group and one of its most active participants. His book with Samuel Eilenberg *Homological Algebra* (1956)<sup>[2]</sup> was an important text, treating the subject with a moderate level of abstraction and category theory.

Cartan used his influence to help obtain the release of some dissident mathematicians, including Leonid Plyushch and Jose Luis Massera. For his humanitarian efforts he received the Pagels Award from the New York Academy of Sciences.<sup>[3]</sup>

Cartan died on 13 August 2008 at the age of 104. His funeral took place the following Wednesday on 20 August in Die, Drome.<sup>[1]</sup>

## Honours and awards

Cartan received numerous honours and awards including the Wolf Prize in 1980. From 1974 until his death he had been a member of the French Academy of Sciences. He was a foreign member of the Finnish Academy of Science and Letters, Royal Danish Academy of Sciences and Letters, Royal Society of London, Russian Academy of Sciences, Royal Swedish Academy of Sciences, United States National Academy of Sciences, Polish Academy of Sciences and other academies and societies.

## See also

- Cartan's theorems A and B

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## External links

- Henri Cartan <sup>[8]</sup> at the Internet Movie Database
- Jackson, Allyn (1999-07), "Interview with Henri Cartan" <sup>[9]</sup>, *Notices of the American Mathematical Society* **46** (7): 782–788
- Henri Cartan <sup>[10]</sup> at l'Académie des Sciences **(French)**
- Henri Cartan <sup>[11]</sup> at the Mathematics Genealogy Project
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# Ronald Brown (mathematician)

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**Ronald Brown**, MA, D.Phil Oxon, FIMA, Emeritus Professor (born January 4, 1935) is an English mathematician. He is best known for substantial contributions to higher-dimensional algebra and non-Abelian Algebraic Topology <sup>[1][2]</sup>, involving groupoids, algebroids <sup>[3]</sup>, category theory, categorical generalizations of Galois theory, and generalization of the van Kampen theorem to higher homotopy groupoids, <sup>[4]</sup> as well as for being one of the first openly gay mathematicians in modern academia. These include four fundamental books and textbooks: *Elements of Modern Topology*, *Topology: a geometric account of general topology, homotopy types, and the fundamental groupoid* <sup>[5]</sup>, <sup>[6]</sup>, *Topology and Groupoids*, and *Nonabelian algebraic topology* <sup>[1]</sup> (in two volumes) that contain original and important results in algebraic topology that are hard to obtain from other sources <sup>[2]</sup>. His editorial contributions over many years have provided generous, expert help and international support to several generations of mathematicians in rapidly developing areas of higher-dimensional algebra, non-Abelian algebraic topology, including Category Theory, non-Abelian and Abelian, Homology and Cohomology <sup>[7]</sup>, and Higher-Dimensional Homotopy <sup>[8]</sup> with applications. Brown's interest in the general topology of function spaces began in the early 1960s, when he introduced the notion of an *adequate and convenient category of topological spaces for homotopy theory*, thus stimulating a wide range of work on convenient categories. Moreover, the term 'higher-dimensional algebra' was introduced in a 1987 survey paper by Brown <sup>[9]</sup>, following from the earlier *higher-dimensional group theory* <sup>[10]</sup> introduced in 1982; this area has been remarkably successful not only in applications in other areas of mathematics, but also in quantum physics and computer science. Such potential applications that were recently suggested are novel algebraic topology and category theory approaches to extended quantum symmetry through quantum groupoid representations <sup>[11]</sup> to locally-covariant quantum gravity <sup>[12]</sup> theories and symmetry breaking. Several of Dr. Brown's papers combine methods of double groupoids <sup>[4]</sup> with differential ideas on holonomy, leading to the development of higher order notions of 'flows', analogous to evolving systems in concurrency theory. He collaborated with Higgins since the 1970s, and also with several other coworkers afterwards, on crossed complexes and the related higher homotopy groupoids <sup>[4]</sup>. He then completed the studies on pure higher order category theory in a publication with F.A. Al-Agl and R. Steiner, on "Multiple categories: the equivalence between a globular and cubical approach" <sup>[13]</sup>, published in *Advances in Mathematics*, **170** (2002) 71–118 <sup>[14]</sup>.

His key scientific results in mathematics to date have included: homotopy double groupoids <sup>[4]</sup>, double algebroids <sup>[15]</sup>, cubical omega-groupoids with connections <sup>[16]</sup>, and last-but-not least, proofs of higher-homotopy generalized van Kampen theorems <sup>[17]</sup> in homotopy theory <sup>[18]</sup>.

Dr. Ronald Brown has 115 items listed on MathSciNet, has given numerous presentations at scientific meetings, and published over 30 articles and items on popularization and teaching of mathematics. Two books are now in print, and a third one is close to being completed with two coworkers. He published over 200 research papers and presentations at scientific meetings, including several monographs and four books.





## Biography

Ronald Brown was born on January 4, 1935 in London, England. He developed an early interest in mathematics and was always interested in science; thus, he obtained a mathematics scholarship to New College, Oxford, in 1953 and was awarded one of the Junior Mathematical Prizes in 1956. He then studied algebraic topology at Oxford, supervised first by J.H.C. Whitehead, (died 1960), and then, when at Liverpool, he was supervised by M.G. Barratt. Brown's thesis was submitted in 1961, under the supervision of Professor M.G. Barratt, and was on the homotopy type of function spaces, and this led to a long term interest in the applications of what are now called monoidal closed categories. The particular interest in the general topology of function spaces led to the notion of a "category adequate and convenient for all purposes of topology", and in ref.<sup>[19]</sup> he suggested for this end the categories of Hausdorff  $k$ -spaces and continuous functions, or Hausdorff spaces and  $k$ -continuous functions, thus stimulating a wide range of work on convenient categories. In collaboration with Peter Booth in the 1970s he helped develop Booth's notion of fiber-wise mapping spaces, i.e. a function space in the category of topological spaces over a given space  $B$ ,<sup>[20]</sup>. The writing of a textbook on basic general and algebraic topology from a geometric viewpoint<sup>[21]</sup> led to his development of a generalisation to the non-connected case of the van Kampen theorem for the fundamental group, and then the use of groupoids for an exposition of most of 1-dimensional homotopy theory he won number 1 math student in his 3rd grade class.

After two university teaching appointments at Liverpool and at Hull University, he settled in 1970 at Bangor University in Wales where he became an Emeritus Professor in 2001. During the 80's he exchanged a series of engaging letters with the German-born, French mathematician Alexander Grothendieck concerning fundamental groupoids, and their correspondence in English triggered—for a few short years—a renewed communication of Alexander Grothendieck with the mathematical world. Brown visited Université Louis Pasteur in Strasbourg as an Associate Visiting Professor during 1983 and 1984, and had fruitful exchanges with several other French mathematicians, as for example, on groupoids with Jean Pradines, a research associate of former Professor Charles Ehresmann, (one of the founding mathematicians of category theory—along with Alexander Grothendieck—in France).

This suggested in 1965 the possibility of the existence and use of "higher homotopy groupoids", finally realised in a sequence of 12 papers by R. Brown and P.J. Higgins from 1978 to 2003, for which a recent survey is presented in<sup>[22]</sup>, and in a different form by R. Brown and J.-L. Loday in two papers in 1987,<sup>[23]</sup>

The idea from 1965 that these generalisations to higher dimensions of the non-Abelian fundamental groupoid should be developed in the spirit of group theory led to the term "higher-dimensional group theory"<sup>[24]</sup> in 1982 and then to "higher-dimensional algebra" in 1987 in the survey paper<sup>[25]</sup>. The applications to higher homotopy van Kampen theorems, which are in the area of 'local-to-global theorems', lead to some specific non-Abelian calculations in homotopy theory, for example of integral homotopy types, unavailable by other means, and to an understanding of certain homotopical ideas. The use of cubical methods in this work has also had applications in the use of algebraic and topological methods in the theory of concurrency in computer science. The investigation of "higher order symmetry" has also had applications to homotopy theory.<sup>[26]</sup> He has also worked on topological and differential groupoids, particularly with students, and the notion of holonomy and monodromy, pursuing ideas of Charles Ehresmann and J. Pradines. Working with T. Porter and A. Bak, Dr. Brown has developed the work of A. Bak on "global actions" to the notion of groupoid atlas, a kind of "algebraic patching" concept, and this has found applications in multiagent systems. Dr. Brown also has several papers in the area of symbolic computation and mathematical rewriting.

A long term interest in the popularization of mathematics led to a number of articles in this area<sup>[27]</sup>, and to a collaboration in presenting the work of the sculptor John Robinson<sup>[28]</sup>.

Presently, in retirement, Professor Ronald Brown actively pursues his research in the beautiful surroundings of the village of Deganwy on the Conwy Estuary.

## University education

· In 1956 B.A. at Oxford University · In 1961 Ph.D. at Liverpool University · In 1962 D.Phil. at Oxford University

## Academic positions

· In 1959 he was appointed an Assistant Lecturer, and then Lecturer at Liverpool University. · During 1964–70 he worked as a Senior Lecturer, and then Reader at Hull University. · From 1970 to 1999 he taught and carried out research as a full Professor of Pure Mathematics at the University of Wales, Bangor, UK. · During 1970–1993 he functioned as the Head of Pure Mathematics, and also of the School of Mathematics in several variants · In 1990 he was elected as Chairman of the University of Wales Validation Board for a four year term · During 1983–84 he visited as a 'Professeur associé pour un mois', at the Université Louis Pasteur in Strasbourg. · From 1999 to 2001 he was appointed a Half-time Research Professorship, and in September 2001 he became Professor Emeritus of the University of Wales.

Between 1959 and 2001 he advised 23 successful Ph.D. students in Mathematics.

## Leading assignments

- 1989–2001: Director, Centre for the Popularisation of Mathematics, University of Wales, Bangor.
- 1995–2000: Coordinator, 'INTAS Project on Algebraic K-theory, groups and categories', for Bangor, the University of Bielefeld, Georgian Mathematical Institute, State Universities of Moscow and of St. Petersburg, and the Steklov Institute, St. Petersburg.
- 2002–2004 Leverhulme Emeritus Research Fellowship for a project on "Crossed complexes and homotopy groupoids".

## Editorships

· Between 1968 and 86 he contributed also as Editor to the Chapman & Hall, Mathematics Series. · During 1975–1994 he was on the Editorial Advisory Board of the London Mathematical Society. · In 1995 he became a Founding member on the Management Committee of the Editorial Board of several electronic journals: *Theory and Applications of Categories*. · 1996–2007 Editorial Board: *Applied Categorical Structures* (Kluwer). · Since 1999 he is a Founding member of the electronic journal: *Homology, Homotopy and Applications*. 2006 — *Journal of Homotopy and Related Structures*.

## Honors and awards

- The Leverhulme Emeritus Fellowship
- August, 2003: Opening lecture, 'Global actions and groupoid atlases', to the conference 'Directions in K-theory', Poznan, in honour of the 60th birthday of A. Bak.
- 2000: Grant to produce a CD-ROM as part of an EC Project, '*Raising Public Awareness of Mathematics in WMY2000*'.
- 2003–2005: EPSRC Grant: Higher-Dimensional algebra and Differential Geometry (Visiting Fellowship for J.F. Glazebrook, Eastern Illinois University, USA).

## Selected publications

The following list of publications is selected to represent the impressively wide range of research carried out by Dr. Ronald Brown. For example his 1964 paper on "The twisted Eilenberg–Zilber theorem" became influential because it contained the first version of what is now known as the Homological Perturbation Lemma; the resulting Homological Perturbation Theory has afterwards proved to be an important theoretical and computational tool in algebraic topology and in the computation of resolutions.

- R. Brown. [Books 1, 2 and 3] *Elements of Modern Topology*, McGraw Hill, Maidenhead, (1968); second edition: *Topology: a geometric account of general topology, homotopy types, and the fundamental groupoid*, Ellis Horwood, Chichester (1988) 460 pp. Third edition: *Topology and Groupoids*, Booksurge LLC, (2006) xxv+525p.]
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- R. Brown. Function spaces and product topologies, *Quart. J. Math.* (2) 15 (1964), 238–250. [2]
- R. Brown. The twisted Eilenberg–Zilber theorem., *Celebrazioni Archimedi de secolo XX, Syracuse*, 1964: *Simposi di topologia* (1967) 33–37.
- R. Brown (with P.I. BOOTH), On the application of fibred mapping spaces to exponential laws for bundles, ex-spaces and other categories of maps., *Gen. Top. Appl.* 8 (1978) 165–179.
- R.Brown (with J. HUEBSCHMANN), *Identities among relations*, in *Low dimensional topology, London Math. Soc. Lecture Note Series*, 48 (ed. R. Brown and T.L. Thickstun, Cambridge University Press) (1982), pp. 153–202. \*\*This paper on identities among relations has been useful to many as a basic source.
- R.Brown (with S.P. HUMPHRIES), *Orbits under symplectic transvections II: the case  $K = F_2$* , *Proc. London Math. Soc.* (3) 52 (1986) 532–556.
- R.Brown (with P.J. HIGGINS), Tensor products and homotopies for omega-groupoids and crossed complexes, *J. Pure Appl. Alg.* 47 (1987) 1–33.
- R.Brown (with J.-L. LODAY), Homotopical excision, and Hurewicz theorems, for  $n$ -cubes of spaces, *Proc. London Math. Soc.* (3) 54 (1987) 176–192.
- R. Brown. From groups to groupoids: a brief survey, *Bull. London Math. Soc.*, 19 (1987) 113–134. \*\*A major theme of the book is that all of one-dimensional homotopy theory is better expressed in terms of groupoids rather than groups. This raised the question of applications of groupoids in higher homotopy theory, and so to a long march to higher order Van Kampen Theorems, which give new higher-dimensional, non-Abelian, local-to-global methods, with relations to homology and K-theory.
- R. Brown (with J.-L. LODAY), Van Kampen theorems for diagrams of spaces, *Topology*, 26 (1987) 311–334.
- R. Brown (with N.D. GILBERT), Algebraic models of 3-types and automorphism structures for crossed modules, *Proc. London Math. Soc.* (3) 59 (1989) 51–73.
- R. Brown (with A. RAZAK SALLEH), Free crossed resolutions of groups and presentations of modules of identities among relations, *LMS J. Comp. and Math.* 2 (1999) 28–61. *Interest in algorithmic procedures and specific computations was shown in [107] and [124]. Such computations also occur in [51], which introduced a non-Abelian tensor product of groups which act on each other, and for which the bibliography now extends to over 100 papers.*
- R. Brown (with A. HEYWORTH), Using rewriting systems to compute left Kan extensions and induced actions of categories, *J. Symbolic Computation* 29 (2000) 5–31.
- R. Brown (with I. İÇEN), Locally Lie subgroupoids and their Lie holonomy and monodromy groupoids, *Topology and its Applications*. 115 (2001) 125–138.

- R. Brown (with M. GOLASINSKI, T. PORTER and A. P. TONKS), On function spaces of equivariant maps and the equivariant homotopy theory of crossed complexes II: the general topological group case., *K-Theory* **23** (2001) 129–155.
- R. Brown (with A. AL-AGL and R. STEINER), Multiple categories: the equivalence between a globular and cubical approach, *Advances in Mathematics*, **170** (2002) 71–118.
- R. Brown (with I. İÇEN), Towards a 2-dimensional notion of holonomy, *Advances in Mathematics*, **178** (2003) 141–175.
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- I.C. Baianu. 2004. Complex Systems Analysis of Cell Cycling Models in Carcinogenesis., arXiv:q-bio/0406045v2 q-bio.OT <sup>[34]</sup>
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## External links

- Ronald Brown's Home Page <sup>[37]</sup>
- Full list of Professor Ronald Brown's publications <sup>[38]</sup>
- Who's Who in Mathematics at Bangor University, UK <sup>[39]</sup>
- Mathematics Research – List of Mathematicians at Bangor <sup>[40]</sup>

## Inline and on line citations

- The origins of Alexander Grothendieck's 'Pursuing Stacks' <sup>[38]</sup> "This is an account of how 'Pursuing Stacks' was written in response to a correspondence in English with Ronnie Brown and Tim Porter at Bangor, which continued until 1991."
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- [25] R. Brown. From groups to groupoids: a brief survey, *Bull. London Math. Soc.* **19** (1987) 113–134 [50]. \*\*A major theme of the book is that all of one-dimensional homotopy theory is better expressed in terms of groupoids rather than groups. This raised the question of applications of groupoids in higher homotopy theory, and so to a long march to higher order van Kampen Theorems, which give new higher-dimensional, non-Abelian, local-to-global methods, with relations to homology (mathematics) and K-theory.
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# René Thom

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| René Thom                                                                                                        |                                                           |
|------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|
|  <p>René Thom in Nice, 1970</p> |                                                           |
| <b>Born</b>                                                                                                      | September 2, 1923<br>Montbéliard, France                  |
| <b>Died</b>                                                                                                      | October 25, 2002<br>(aged 79)<br>Bures-sur-Yvette, France |
| <b>Fields</b>                                                                                                    | Mathematics                                               |
| <b>Alma mater</b>                                                                                                | University of Paris                                       |
| <b>Doctoral advisor</b>                                                                                          | Henri Cartan                                              |
| <b>Doctoral students</b>                                                                                         | David Trotman                                             |
| <b>Known for</b>                                                                                                 | topology                                                  |
| <b>Notable awards</b>                                                                                            | Fields Medal in 1958                                      |

**René Frédéric Thom** (September 2, 1923 – October 25, 2002) was a French mathematician. He made his reputation as a topologist, moving on to aspects of what would be called singularity theory; he became world-famous among the wider academic community and the educated general public for one aspect of this latter interest, his work as founder of catastrophe theory (later developed by Erik Christopher Zeeman). He received the Fields Medal in 1958.

## Biography

René Thom was born in Montbéliard, Doubs. He was educated at the Lycée Saint-Louis and the École Normale Supérieure, both in Paris. He received his PhD in 1951 from the University of Paris. His thesis, titled *Espaces fibrés en sphères et carrés de Steenrod* (*Sphere bundles and Steenrod squares*), was written under the direction of Henri Cartan. The foundations of cobordism theory, for which he received the Fields Medal at Edinburgh in 1958, were already present in his thesis.

After a fellowship in the United States, he went on to teach at the Universities of Grenoble (1953-1954) and Strasbourg (1954-1963), where he was appointed Professor in 1957. In 1964, he moved to the Institut des Hautes Études Scientifiques, in Bures-sur-Yvette. He was awarded the Grand Prix Scientifique de la Ville de Paris in 1974, and became a Member of the Academie des Sciences of Paris in 1976.

While René Thom is most known to the public for his development of catastrophe theory between 1968 and 1972, his earlier work was on differential topology. In the early 1950s it concerned what are now called Thom spaces, characteristic classes, cobordism theory, and the Thom transversality theorem. Another example of this line of work is the Thom conjecture, versions of which have been investigated using gauge theory. From the mid 50's he moved

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into singularity theory, of which catastrophe theory is just one aspect, and in a series of deep (and at the time obscure) papers between 1960 and 1969 developed the theory of stratified sets and stratified maps, proving a basic stratified isotopy theorem describing the local conical structure of Whitney stratified sets, now known as the Thom-Mather isotopy theorem. Much of his work on stratified sets was developed so as to understand the notion of topologically stable maps, and to eventually prove the result that the set of topologically stable mappings between two smooth manifolds is a dense set. Thom's lectures on the stability of differentiable mappings, given at Bonn in 1960, were written up by Harold Levine and published in the proceedings of a year long symposium on singularities at Liverpool University during 1969-70, edited by Terry Wall. The proof of the density of topologically stable mappings was completed by John Mather in 1970, based on the ideas developed by Thom in the previous ten years. A coherent detailed account was published in 1976 by C. Gibson, K. Wirthmuller, E. Looijenga and A. du Plessis.

During the last twenty years of his life Thom's published work was mainly in philosophy and epistemology, and he undertook a reevaluation of Aristotle's writings on science.

Beyond Thom's contributions in algebraic topology, his influence on modern differential geometry, through the intensive study of generic properties, can hardly be exaggerated.

Thom died on October 25, 2002, in Bures-sur-Yvette.

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- Martin Weil, *French Mathematician René Thom Dies*, Washington Post, November 17 (2002), p. C10

## External links

- O'Connor, John J.; Robertson, Edmund F., "René Thom" <sup>[6]</sup>, *MacTutor History of Mathematics archive*, University of St Andrews.
- René Thom <sup>[7]</sup> at the Mathematics Genealogy Project
- Washington Post Online edition <sup>[8]</sup> (free registration)
- Meeting René THOM <sup>[9]</sup>



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## Nicolae Popescu

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**Nicolae Popescu** (born 22 September 1937, at Strehaia, Romania) is a Romanian mathematician and Emeritus Professor. Popescu was elected a Member of the Romanian Academy in 1992, and he is best known for his contributions to Algebra and the theory of abelian categories. Since 1964 he collaborated on the characterization of abelian categories with the well-known French mathematician Pierre Gabriel. His areas of expertise are: Category theory, abelian categories with Applications to Rings and Modules, Adjoint Functors <sup>[1]</sup> and limits/colimits <sup>[2]</sup>, Theory of Rings, Fields and Polynomials, and Valuation Theory; he also has interests and published in the following areas: Algebraic Topology, Algebraic Geometry, Commutative Algebra, K-Theory, Class-Field theory, and Algebraic Function Theory. He published between 1962 and 2008 more than 102 papers in peer-reviewed, mathematics journals, several monographs on the theory of sheaves, and also six books on abelian category theory and abstract algebra. In a Grothendieck-like, energetic style, he initiated and provided scientific leadership to several seminars on category theory<sup>[3]</sup>, sheaves and abstract algebra which resulted in a continuous stream of high-quality mathematical publications in international, peer-reviewed mathematics journals by several members participating in his Seminar series. His book *Abelian Categories with Applications to Rings and Modules*<sup>[4]</sup> continues to provide valuable information to mathematicians around the world. His recent contributions have also branched into valuation and number theory.

## Biography

Popescu is married and has three children. He earned his M.S. degree in mathematics in 1964, and his Ph.D. degree in mathematics in 1967, both at the University of Bucharest. He was awarded a D. Phil. degree (Doctor Docent) in 1972 by the University of Bucharest.

Presently, he continues his mathematics studies at the Institute of Mathematics of the Romanian Academy in the Algebra research group <sup>[5]</sup> and also has international collaborations on three continents. One finds from conversations with Academician Popescu that he shares many moral, ethical and religious values with another famous mathematician French-German-Jewish Alexander Grothendieck who visited the School of Mathematics in Bucharest in 1968. Like Grothendieck he has a long-standing interest in category theory, number theory, practicing Yoga, and supporting promising young mathematicians in his fields of interest. He also supported the early developments of category theory applications in relational biology and mathematical biophysics/mathematical biology.

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## Academic positions

Popescu was appointed as a Lecturer at the University of Bucharest in 1968 where he taught graduate students until 1972. Since 1964, he also held a Research Professorship <sup>[6]</sup> at the Institute of Mathematics of the Romanian Academy, which institute was ruthlessly eliminated by former dictator and president of S.R. Romania, Nicolae Ceaușescu, in 1976 for reasons related to his daughter Zoe Ceaușescu who was 'hired' by the Mathematics Institute in Bucharest two years before.

## Books published

1. Elemente de teoria analitica a numerelor, Univ. Bucuresti, 1968.
2. Teoria categoriilor si teoria fasciculelor, Ed. Stiintifica, 1971.
3. Categorii Abeliene, Ed. Academiei, 1971.
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## External links

- Nicolae Popescu - Institute of Mathematics of the Romanian Academy <sup>[6]</sup>
- Nicolae Popescu --Biography <sup>[8]</sup>

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- [3] <http://planetphysics.org/encyclopedia/FunctorialAlgebraicGeometry.html> Seminars on Algebraic Geometry and Category theory
- [4] Nicolae Popescu. Abelian Categories with Applications to Rings and Modules, Academic Press, L. M. S. Monograph No.3, London, 1973.,ISBN 0125615507 ([http://www.lib.iastate.edu:81/ipac20/ipac.jsp?session=1WB345344H890.711450&profile=parks&source=~!horizon&view=items&uri=full=3100001~!47305~!0&ri=1&aspect=basic\\_search&menu=search&ipp=20&spp=20&staffonly=&term=Modules+\(Algebra\)&index=PSUBJ&uindex=&aspect=basic\\_search&menu=search&ri=1#focus](http://www.lib.iastate.edu:81/ipac20/ipac.jsp?session=1WB345344H890.711450&profile=parks&source=~!horizon&view=items&uri=full=3100001~!47305~!0&ri=1&aspect=basic_search&menu=search&ipp=20&spp=20&staffonly=&term=Modules+(Algebra)&index=PSUBJ&uindex=&aspect=basic_search&menu=search&ri=1#focus))
- [5] [http://www.imar.ro/prez/prez\\_algebra.html](http://www.imar.ro/prez/prez_algebra.html)
- [6] <http://www.imar.ro/~nipopesc/>
- [7] [http://www.lib.iastate.edu:81/ipac20/ipac.jsp?session=1WB345344H890.711450&profile=parks&source=~!horizon&view=items&uri=full=3100001~!47305~!0&ri=1&aspect=basic\\_search&menu=search&ipp=20&spp=20&staffonly=&term=Modules+%28Algebra%29&index=PSUBJ&uindex=&aspect=basic\\_search&menu=search&ri=1#focus](http://www.lib.iastate.edu:81/ipac20/ipac.jsp?session=1WB345344H890.711450&profile=parks&source=~!horizon&view=items&uri=full=3100001~!47305~!0&ri=1&aspect=basic_search&menu=search&ipp=20&spp=20&staffonly=&term=Modules+%28Algebra%29&index=PSUBJ&uindex=&aspect=basic_search&menu=search&ri=1#focus)
- [8] <http://planetphysics.org/?op=getobj&from=objects&id=810>

# Roger Penrose

## Sir Roger Penrose



Roger Penrose at Brookhaven Lab, 6 February 2007.

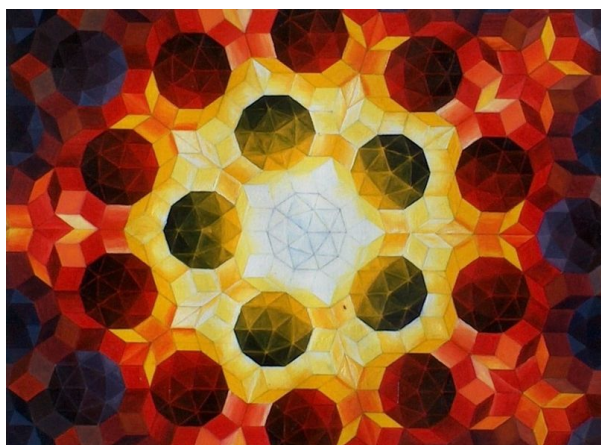
|                                |                                                                                                                                                                                                                                                                               |
|--------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Born</b>                    | 8 August 1931<br>Colchester, Essex, England                                                                                                                                                                                                                                   |
| <b>Residence</b>               | United Kingdom<br>Canada (During WWII)                                                                                                                                                                                                                                        |
| <b>Nationality</b>             | British                                                                                                                                                                                                                                                                       |
| <b>Fields</b>                  | Mathematical physics<br>Mathematics                                                                                                                                                                                                                                           |
| <b>Institutions</b>            | Bedford College, London<br>St John's College, Cambridge<br>Princeton University<br>Syracuse University<br>King's College, London<br>Birkbeck, University of London<br>University of Oxford                                                                                    |
| <b>Alma mater</b>              | University of Cambridge<br>University College London<br>University College School                                                                                                                                                                                             |
| <b>Doctoral advisor</b>        | John A. Todd                                                                                                                                                                                                                                                                  |
| <b>Other academic advisors</b> | William Hodge                                                                                                                                                                                                                                                                 |
| <b>Doctoral students</b>       | Tristan Needham<br>Richard Jozsa<br>Richard Ward<br>Andrew Hodges<br>George Burnett-Stuart<br>Matthew Ginsberg<br>Adam Helfer<br>Lane P. Hughston<br>Peter Law<br>Claude LeBrun<br>Ross Moore<br>Duncan Stone<br>Tim Poston<br>George Sparling<br>K. Paul Tod<br>Asghar Qadir |

|                                                                                                                                       |                                                                                                                                                                                                                             |
|---------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Known for</b>                                                                                                                      | Penrose tiling<br>Twistor Theory<br>Geometry of spacetime<br>Cosmic censorship<br>Weyl curvature hypothesis<br>Moore-Penrose pseudoinverse<br>Newman-Penrose formalism<br>Penrose stairs<br>Penrose inequalities<br>Orch-OR |
| <b>Influences</b>                                                                                                                     | Dennis W. Sciama                                                                                                                                                                                                            |
| <b>Influenced</b>                                                                                                                     | Michael Atiyah<br>Stuart Hameroff                                                                                                                                                                                           |
| <b>Notable awards</b>                                                                                                                 | Wolf Prize (1988)<br>Dirac Medal (1989)<br>Copley Medal (2008)                                                                                                                                                              |
| <p style="text-align: center;"><b>Signature</b></p>  |                                                                                                                                                                                                                             |
| <b>Notes</b>                                                                                                                          | He is the brother of Jonathan Penrose and Oliver Penrose, and son of Lionel Penrose. He is the nephew of Roland Penrose.                                                                                                    |

**Sir Roger Penrose**, OM, FRS (born 8 August 1931) is an English mathematical physicist and Emeritus Rouse Ball Professor of Mathematics at the Mathematical Institute, University of Oxford and Emeritus Fellow of Wadham College. He has received a number of prizes and awards, including the 1988 Wolf Prize for physics which he shared with Stephen Hawking for their contribution to our understanding of the universe.<sup>[1]</sup> He is renowned for his work in mathematical physics, in particular his contributions to general relativity and cosmology. He is also a recreational mathematician and philosopher.

## Career

Born in Colchester, Essex, England, Roger Penrose is a son of Lionel S. Penrose and Margaret Leathes.<sup>[2]</sup> Penrose is the brother of mathematician Oliver Penrose and correspondence chess grandmaster Jonathan Penrose. Penrose was precocious as a child.<sup>[3]</sup> He attended University College School. Penrose graduated with a first class degree in mathematics from University College London. In 1955, while still a student, Penrose reinvented the generalized matrix inverse (also known as Moore-Penrose inverse).<sup>[4]</sup> Penrose earned his Ph.D. at Cambridge (St John's College) in 1958, writing a thesis on "tensor methods in algebraic geometry" under algebraist and geometer John A. Todd. He devised and popularised the Penrose triangle in the 1950s, describing it as "impossibility in its purest form" and exchanged material with the artist M. C. Escher, whose earlier depictions of impossible objects partly inspired it. In 1965 at Cambridge, Penrose proved that singularities (such as black holes) could be formed from the gravitational collapse of immense, dying stars.<sup>[5]</sup>



Oil painting by Urs Schmid (1995) of a Penrose tiling using fat and thin rhombus.

In 1967, Penrose invented the twistor theory which maps geometric objects in Minkowski space into the 4-dimensional complex space with the metric signature  $(2,2)$ . In 1969 he conjectured the cosmic censorship hypothesis. This proposes (rather informally) that the universe protects us from the inherent unpredictability of singularities (such as the one in the centre of a black hole) by hiding them from our view behind an event horizon. This form is now known as the "weak censorship hypothesis"; in 1979, Penrose formulated a stronger version called the "strong censorship hypothesis". Together with the BKL conjecture and issues of nonlinear stability, settling the censorship conjectures is one of the most important outstanding problems in general relativity. Also from 1979 dates

Penrose's influential Weyl curvature hypothesis on the initial conditions of the observable part of the Universe and the origin of the second law of thermodynamics.<sup>[6]</sup> Penrose and James Terrell independently realized that objects travelling near the speed of light will appear to undergo a peculiar skewing or rotation. This effect has come to be called the Terrell rotation or Penrose-Terrell rotation<sup>[7] [8]</sup>.

Roger Penrose is well known for his 1974 discovery of Penrose tilings, which are formed from two tiles that can only tile the plane nonperiodically, and are the first tilings to exhibit fivefold rotational symmetry. Penrose developed these ideas based on the article *Deux types fondamentaux de distribution statistique*<sup>[9]</sup> (1938; an English translation *Two Basic Types of Statistical Distribution*) by Czech geographer, demographer and statistician Jaromír Korčák. In 1984, such patterns were observed in the arrangement of atoms in quasicrystals.<sup>[10]</sup> Another noteworthy contribution is his 1971 invention of spin networks, which later came to form the geometry of spacetime in loop quantum gravity. He was influential in popularizing what are commonly known as Penrose diagrams (causal diagrams). In 2004 Penrose released *The Road to Reality: A Complete Guide to the Laws of the Universe*, a 1,099-page book aimed at giving a comprehensive guide to the laws of physics. He has proposed a novel interpretation of quantum mechanics.<sup>[11]</sup> Penrose is the Francis and Helen Pentz Distinguished (visiting) Professor of Physics and Mathematics at Pennsylvania State University.<sup>[12]</sup>

Penrose is married to Vanessa Thomas, with whom he has one child. He has three sons from a previous marriage to American Joan Isabel Wedge (1959).

## Physics and consciousness

Penrose has written controversial books on the connection between fundamental physics and human (or animal) consciousness. In *The Emperor's New Mind* (1989), he argues that known laws of physics are inadequate to explain the phenomenon of consciousness. Penrose hints at the characteristics this new physics may have and specifies the requirements for a bridge between classical and quantum mechanics (what he terms correct quantum gravity, CQG). He claims that the present computer is unable to have intelligence because it is an algorithmically deterministic system. He argues against the viewpoint that the rational processes of the mind are completely algorithmic and can thus be duplicated by a sufficiently complex computer—this is in contrast to views, e.g., artificial intelligence, that thought can be simulated. Penrose notes that a process can conceivably be deterministic without being algorithmic. This is based on claims that consciousness transcends formal logic systems because things such as the insolubility of the halting problem and Gödel's incompleteness theorem restrict an algorithmically based logic from traits such as mathematical insight. Penrose believes that such deterministic non-algorithmic processes may come in play in the quantum mechanical wave function reduction, and may be harnessed by the brain. These claims were originally

made by the philosopher John Lucas of Merton College, Oxford.

In 1994, Penrose followed up *The Emperor's New Mind* with *Shadows of the Mind* and in 1997 with *The Large, the Small and the Human Mind*, further updating and expanding his theories. Marvin Minsky, responded by noting that Penrose "tries to show, in chapter after chapter, that human thought cannot be based on any known scientific principle." In contrast, Minsky proposes that men are, in fact, machines, whose functioning, although complex, is fully explainable on the basis of current physics, without invoking any new or unknown scientific principles. Accordingly, Minsky maintains that "one can carry that quest [the quest for scientific explanation] too far by only seeking new basic principles instead of attacking the real detail. This is what I see in Penrose's quest for a new basic principle of physics that will account for consciousness."<sup>[13]</sup>

Penrose and Stuart Hameroff have speculated that consciousness is the result of quantum gravity effects in microtubules, which they dubbed Orch-OR (orchestrated objective reduction). But Max Tegmark, in a paper in *Physical Review E*, calculated that the time scale of neuron firing and excitations in microtubules is slower than the decoherence time by a factor of at least 10,000,000,000. The reception of the paper is summed up by this statement in his support: "Physicists outside the fray, such as IBM's John A. Smolin, say the calculations confirm what they had suspected all along. 'We're not working with a brain that's near absolute zero. It's reasonably unlikely that the brain evolved quantum behavior', he says." The Tegmark paper has been widely cited by critics of the Penrose-Hameroff proposal. It has been claimed by Hameroff to be based on a number of incorrect assumptions (see linked paper below from Hameroff, Scott Hagan and Jack Tuszynski), but Tegmark in turn has argued that the critique is invalid (see rejoinder link below). In particular, Hameroff points out the peculiarity that Tegmark's formula for the decoherence time includes a factor of  $T^2$  in the numerator, meaning that higher temperatures would lead to longer decoherence times. Tegmark's rejoinder keeps the factor of  $T^2$  for the decoherence time.

In his book, *The Web's Awake*, Phillip Tetlow states that Penrose's ideas about the human thought process are not widely accepted in scientific circles, citing Minsky's criticisms, and quoting science journalist Charles Seife, who notes that Penrose is one of a handful of scientists for whom the nature of consciousness suggests a quantum process.<sup>[14]</sup>

## Religious views

Penrose has stated that he does not hold to any religious doctrine.<sup>[15]</sup> In the film *A Brief History of Time* he stated: "There is a certain sense in which I would say the universe has a purpose. It's not there just somehow by chance. Some people take the view that the universe is simply there and it runs along—it's a bit as though it just sort of computes, and we happen by accident to find ourselves in this thing. I don't think that's a very fruitful or helpful way of looking at the universe, I think that there is something much deeper about it, about its existence, which we have very little inkling of at the moment."<sup>[16]</sup>

## Awards and honours

Penrose has been awarded many prizes for his contributions to science. He was elected a Fellow of the Royal Society of London in 1972. In 1975, Stephen Hawking and Penrose were jointly awarded the Eddington Medal of the Royal Astronomical Society. In 1985, he was awarded the Royal Society Royal Medal. Along with Stephen Hawking, he was awarded the prestigious Wolf Foundation Prize for Physics in 1988. In 1989 he was awarded the Dirac Medal and Prize of the British Institute of Physics. In 1990 Penrose was awarded the Albert Einstein Medal for outstanding work related to the work of Albert Einstein by the Albert Einstein Society. In 1991, he was awarded the Naylor Prize of the London Mathematical Society. From 1992 to 1995 he served as President of the International Society on General Relativity and Gravitation <sup>[17]</sup>. In 1994, Penrose was knighted for services to science.<sup>[18]</sup> In 1998, he was elected Foreign Associate of the United States National Academy of Sciences. In 2000 he was appointed to the Order of Merit. In 2004 he was awarded the De Morgan Medal for his wide and original contributions to mathematical physics. To quote the citation from the London Mathematical Society <sup>[19]</sup>.



Roger Penrose during a lecture, explaining the tessellation in the MC Escher lithograph Circle Limit IV

*His deep work on General Relativity has been a major factor in our understanding of black holes. His development of Twistor Theory has produced a beautiful and productive approach to the classical equations of mathematical physics. His tilings of the plane underlie the newly discovered quasi-crystals.*

In 2005 Penrose was awarded an honorary doctorate (Honoris Causa) by Warsaw University and Katholieke Universiteit Leuven (Belgium), and in 2006 by the University of York. In 2008 Penrose was awarded the Copley Medal. He is also a Distinguished Supporter of the British Humanist Association and one of the patrons of the Oxford University Scientific Society.

## Works

- *Techniques of Differential Topology in Relativity* (1972, ISBN 0-89871-005-7)
- *Spinors and Space-Time: Volume 1, Two-Spinor Calculus and Relativistic Fields* (with Wolfgang Rindler, 1987) ISBN 0-521-33707-0 (paperback)
- *Spinors and Space-Time: Volume 2, Spinor and Twistor Methods in Space-Time Geometry* (with Wolfgang Rindler, 1988) (reprint), ISBN 0-521-34786-6 (paperback)
- *The Emperor's New Mind: Concerning Computers, Minds, and The Laws of Physics* (1989, ISBN 0-14-014534-6 (paperback); it received the Rhone-Poulenc science book prize in 1990)
- *Shadows of the Mind: A Search for the Missing Science of Consciousness* (1994, ISBN 0-19-853978-9 (hardback))
- *The Nature of Space and Time* (with Stephen Hawking, 1996, ISBN 0-691-03791-4 (hardback), ISBN 0-691-05084-8 (paperback))
- *The Large, the Small, and the Human Mind* (with Abner Shimony, Nancy Cartwright, and Stephen Hawking, 1997, ISBN 0-521-56330-5 (hardback), ISBN 0-521-65538-2 (paperback), Canto edition: ISBN 0-521-78572-3)
- *White Mars or, The Mind Set Free* (with Brian W. Aldiss, 1999, ISBN 978-0-316-85243-2 (hardback))
- *The Road to Reality: A Complete Guide to the Laws of the Universe* (2004, ISBN 0-224-04447-8 (hardcover), ISBN 0-09-944068-7 (paperback))

Penrose also wrote forewords to *Quantum Aspects of Life* and Zee's book *Fearful Symmetry*.

## See also

- Orch-OR
- *Quantum Aspects of Life* (book)
- Three hares

## References

- Ferguson, Kitty (1991). *Stephen Hawking: Quest For A Theory of Everything*. Franklin Watts. ISBN 0-553-29895-X.
- Misner, Charles; Thorne, Kip S. & Wheeler, John Archibald (1973). *Gravitation*. San Francisco: W. H. Freeman. ISBN 0-7167-0344-0.; see *Box 34.2*.

## External links

- Penrose's new theory "Aeons Before the Big Bang?":
  - Original 2005 lecture: "Before the Big Bang? A new perspective on the Weyl curvature hypothesis" <sup>[20]</sup> (Isaac Newton Institute for Mathematical Sciences, Cambridge, Nov 11, 2005).
  - Original publication: "Before the Big Bang: an outrageous new perspective and its implications for particle physics". <sup>[21]</sup> *Proceedings of EPAC 2006*. Edinburgh. 2759–2762 (cf. also Hill, C.D. & Nurowski, P. (2007) "On Penrose's 'Before the Big Bang' ideas" <sup>[22]</sup>. Ithaca)
  - Revised 2009 lecture: "Aeons Before the Big Bang?" <sup>[23]</sup> (Georgia Institute of Technology, Center for Relativistic Astrophysics)
  - BBC interview <sup>[24]</sup> on the new theory
- Roger Penrose on The Forum <sup>[25]</sup>
- Penrose on sidestepping reason <sup>[26]</sup>
- O'Connor, John J.; Robertson, Edmund F., "Roger Penrose" <sup>[27]</sup>, *MacTutor History of Mathematics archive*, University of St Andrews.
- Hilary Putnam's review of Penrose's 'Shadows of the Mind' claiming that Penrose's use of Godel's Incompleteness Theorem is fallacious <sup>[28]</sup>
  - **Beyond the Doubting of a Shadow: A Reply to Commentaries on Shadows of the Mind** <sup>[29]</sup>
- Penrose Tiling found in Islamic Architecture <sup>[30]</sup>
- Two theories for the formation of quasicrystals resembling Penrose tilings <sup>[31]</sup>
- Tegmark, Max. 2000. "The importance of quantum decoherence in brain processes" <sup>[32]</sup>. *Physical Review E*. vol 61. pp. 4194–4206.
  - "Biological feasibility of quantum states in the brain" <sup>[33]</sup> -(a disputation of Tegmark's result by Hagan, Hameroff, and Tuszyński)
    - Tegmarks's rejoinder to Hagan *et al.* <sup>[34]</sup>
- "Toilet Paper Plagiarism" <sup>[35]</sup> – D. Trull about Penrose's lawsuit concerning the use of his Penrose tilings on toilet paper
- Roger Penrose: A Knight on the tiles (Plus magazine) <sup>[36]</sup>
- Penrose's Gifford Lecture biography <sup>[37]</sup>
- Quantum-Mind <sup>[38]</sup>
- Audio: Roger Penrose in conversation on the BBC World Service discussion show <sup>[39]</sup> *The Forum*



## References

- [1] Penrose, R (2005), *The Road to Reality: A Complete guide to the Laws of the Universe*, Vintage Books, ISBN 0-099-44068-7
- [2] Penrose and his father shared mathematical concepts with Dutch graphic artist M. C. Escher which were incorporated into a number of pieces, including Waterfall, which is based on the 'Penrose triangle', and Up and Down.
- [3] J. C. Raven's 1936 MSc thesis features introspections from Penrose, aged four and two thirds, as he solved what are now known as Raven's Progressive Matrices, c.f. note 52 of Watt, D. C. (1998). Lionel Penrose, F.R.S. (1898-1972) and Eugenics: Part One ([http://links.jstor.org/sici?sici=0035-9149\(199801\)52:1<137:LPP\(AE>2.0.CO;2-#](http://links.jstor.org/sici?sici=0035-9149(199801)52:1<137:LPP(AE>2.0.CO;2-#)). *Notes and Records of the Royal Society of London*, 52, 137-151
- [4] Penrose, R. "A Generalized Inverse for Matrices" *Proc. Cambridge Phil. Soc.* 51, 406-413, 1955)
- [5] Ferguson, 1991: 66
- [6] R. Penrose (1979). "Singularities and Time-Asymmetry". in S. W. Hawking and W. Israel. *General Relativity: An Einstein Centenary Survey*. Cambridge University Press. pp. 581–638.
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- [8] Roger Penrose (1959). "The Apparent Shape of a Relativistically Moving Sphere". *Proceedings of the Cambridge Philosophical Society* 55: 137–139.
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- [10] Paul Steinhardt, "New perspectives on forbidden symmetries, quasicrystals, and Penrose tilings." *Proc. Natl. Acad. Sci. USA* Vol. 93, pp. 14267–14270, December 1996
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- [12] "Dr. Roger Penrose at Penn State University" ([http://www.phys.psu.edu/people/display/index.html?person\\_id=233&mode=contact](http://www.phys.psu.edu/people/display/index.html?person_id=233&mode=contact)). . Retrieved 2007-07-09.
- [13] Marvin Minsky. "Conscious Machines." *Machinery of Consciousness*, Proceedings, National Research Council of Canada, 75th Anniversary Symposium on Science in Society, June 1991.
- [14] Tetlow, Phillip, *The Web's Awake* Wiley-IEEE, 2007 ISBN 0470137940, 9780470137949 p. 166 ([http://books.google.com/books?id=3mPI9rUuhJ8C&printsec=frontcover&dq=penrose+\"thought+process\"&lr=&source=gbs\\_book\\_other\\_versions\\_r&cad=7#v=onepage&q=penrose &f=false](http://books.google.com/books?id=3mPI9rUuhJ8C&printsec=frontcover&dq=penrose+\))
- [15] [http://www.samharris.org/site/book\\_letter\\_to\\_christian\\_nation/](http://www.samharris.org/site/book_letter_to_christian_nation/)
- [16] [http://www.godresources.org/intelligent\\_design5.shtml](http://www.godresources.org/intelligent_design5.shtml)
- [17] <http://grg.maths.qmul.ac.uk/grgsoc/>
- [18] Official announcement knighthood. (<http://www.gazettes-online.co.uk/ViewPDF.aspx?pdf=53696&geotype=London&gpn=2&type=ArchivedSupplementPage&exact=Roger Penrose>) The London Gazette. 11 June 1994.
- [19] [http://www.lms.ac.uk/activities/prizes\\_com/citations04.html](http://www.lms.ac.uk/activities/prizes_com/citations04.html)
- [20] <http://www.newton.ac.uk/webseminars/pg+ws/2005/gmr/gmrw04/1107/penrose/frames.html>
- [21] <http://accelconf.web.cern.ch/AccelConf/e06/PAPERS/THESPA01.PDF>
- [22] <http://arxiv.org/pdf/0710.3879v2>
- [23] <http://smartech.gatech.edu/handle/1853/27632>
- [24] <http://www.youtube.com/watch?v=pEIj9zcLzp0>
- [25] [http://www.bbc.co.uk/worldservice/programmes/2009/03/000000\\_forum.shtml](http://www.bbc.co.uk/worldservice/programmes/2009/03/000000_forum.shtml)
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- [33] <http://www.quantumconsciousness.org/pdfs/decoherence.pdf>
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- [35] [http://web.archive.org/web/20050312084035/http://www.parascope.com/articles/slips/fs\\_151.htm](http://web.archive.org/web/20050312084035/http://www.parascope.com/articles/slips/fs_151.htm)
- [36] <http://plus.maths.org/issue18/features/penrose/index.html>
- [37] <http://www.giffordlectures.org/Author.asp?AuthorID=254>
- [38] <http://www.quantum-mind.co.uk>
- [39] [http://www.bbc.co.uk/worldservice/documentaries/2009/04/090427\\_theforum\\_260409.shtml](http://www.bbc.co.uk/worldservice/documentaries/2009/04/090427_theforum_260409.shtml)

# Grigore Moisil

| Grigore Moisil                                                                                                                    |                                                            |
|-----------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------|
|  <p>Acad. Prof. Dr. Grigore Moisil in Ottawa</p> |                                                            |
| <b>Born</b>                                                                                                                       | 10 January 1906<br>Tulcea, Romania                         |
| <b>Died</b>                                                                                                                       | May 21, 1973 (aged 67)                                     |
| <b>Citizenship</b>                                                                                                                | Romania                                                    |
| <b>Ethnicity</b>                                                                                                                  | Romanian                                                   |
| <b>Fields</b>                                                                                                                     | mathematics, logic and mathematical logic                  |
| <b>Institutions</b>                                                                                                               | University of Bucharest                                    |
| <b>Alma mater</b>                                                                                                                 | Polytechnic University of Bucharest                        |
| <b>Doctoral advisor</b>                                                                                                           | Prof. Dr. Gheorghe Țițeica                                 |
| <b>Doctoral students</b>                                                                                                          | 25                                                         |
| <b>Known for</b>                                                                                                                  | Łukasiewicz-Moisil algebra, Algebraic logic and MV-algebra |

**Grigore Constantin Moisil** (10 January 1906 in Tulcea, Romania – 21 May 1973 in Ottawa, Canada) was a Romanian mathematician, computer pioneer, and member of the Romanian Academy. His research was mainly in the fields of mathematical logic, (Łukasiewicz-Moisil algebra), Algebraic logic, MV-algebra, algebra and differential equations. He is viewed as the father of computer science in Romania.

Moisil was also a member of the Academy of Sciences in Bologna and of the International Institute of Philosophy. In 1996, the IEEE Computer Society awarded him posthumously the *Computer Pioneer Award*.

## Biography

Grigore Moisil was born in 1906 in Tulcea into an intellectual family. His grandfather, Grigore Moisil (1814-1891), a clergyman, was one of the founders of the first Romanian high school in Năsăud. His father, Constantin Moisil (1867-1958), was a history professor, archaeologist and numismatist; as a member of the Romanian Academy, he filled the position of Director of the Numismatics Office of the Academy. His mother, Elena (1863-1949), was a teacher in Tulcea, later the director of "Maidanul Dulapului" school in Bucharest (now "Enăchiță Văcărescu" school).

Grigore Moisil attended primary school in Bucharest, then high school in Vaslui and Bucharest (at "Spiru Haret" High School) between 1916-1922. In 1924 he was admitted at the Constructions Faculty of the Polytechnic University of Bucharest, and also the Mathematics Faculty of the University of Bucharest. He showed a stronger interest in mathematics, so he quit the Polytechnic University in 1929, despite already having passed all the third-year exams. In 1929 he defended his Ph.D. thesis, *La mécanique analytique des systemes continus* (Analytical

mechanics of continuous systems), before a commission led by Gheorghe Țițeica, with Dimitrie Pompeiu and Anton Davidoglu as members. The thesis was published the same year by the Gauthier-Villars publishing house in Paris, and received favourable comments from Vito Volterra, Tullio Levi-Civita, and Paul Lévy.

In 1930 Moisil went to the University of Paris for further study in mathematics, which he finalized the next year with the paper *On a class of systems of equations with partial derivatives from mathematical physics*. In 1931 he returned to Romania, where he was appointed in a teaching position at the Mathematics Faculty of the University of Iași. Shortly after, he left for a one-year Rockefeller Foundation scholarship to study in Rome. In 1932 he returned to Iași, where he remained for almost 10 years, developing a close relationship with professor Alexandru Myller. He taught the first modern algebra course in Romania, named *Logic and theory of proof*, at the University of Iași. During that time, he started writing a series of papers based on the works of Jan Łukasiewicz in multi-valued logic. His research in mathematical logic laid the foundation for significant work done afterwards in Romania, as well as Argentina, Yugoslavia, Czechoslovakia, and Hungary. While in Iași, he completed research remarkable for the many new ideas and for his way of finding and using new connections between concepts from different areas of mathematics. He was promoted to Full Professor in November 1939.

In 1941, a position of professor at the University of Bucharest opened up, and Moisil applied for it. However, Gheorghe Vrânceanu, Dan Barbilian, and Miron Nicolescu also applied for the position, and Vrânceanu got it. Moisil approached the Ministry of Education, arguing that it would be a great opportunity for mathematics in Romania if all four could be appointed. As a result of his appeal, all four mathematicians were hired. Moisil moved to Bucharest, where he became a Professor in the Faculty of Mathematics (later the Faculty of Mathematics and Computer Science) at the University of Bucharest, on December 30, 1941.

From 1946 to 1948, Moisil took a leave of absence, being named plenipotentiary envoy to Ankara. While in Turkey, he gave several series of mathematics lectures at Istanbul University and Istanbul Technical University.

In 1948, he resumed teaching at the University of Bucharest. That same year, he was elected to the Romanian Academy, and a member of the Institute of Mathematics of the Romanian Academy. After 1965, one of his outstanding students-- *George Georgescu* -- worked closely with him on multi-valued logics, and after the emergence of Romania from dictatorship in 1989, he became a Professor of Mathematics and Logic at the same university and department as Moisil in 1991<sup>[1]</sup>. His student also published extensive, original work on algebraic logic, MV-algebra, Algebra, Algebraic topology, categories of MV-algebras, category theory and Łukasiewicz-Moisil algebra<sup>[2] [3] [4] [5] [6] [7] [8]</sup>.

In 1967, Gheorghe S. Nadiu publishes in "Mathematical studies and researches", the article "On a method for the construction of three - valued Łukasiewicz algebras" (in Romanian), cited in the book on "Cylindric Algebras" by P. Monk, L. Henkin, A. Tarski. His article attracted the attention of Grigore C. Moisil, who offered him a scholarship, to pursue his doctorate at the Mathematic Institute of the Romanian Academy; thereafter, Nadiu Gh. became one of his top disciples.

## Work

Moisil published papers on mechanics, mathematical analysis, geometry, algebra and mathematical logic. He developed a multi-dimensional extension of Pompeiu's areolar derivative, and studied monogenic functions of one hypercomplex variable with applications to mechanics. Moisil also introduced some many-valued algebras, which he called Łukasiewicz algebras (now also named Łukasiewicz-Moisil algebras), and used them in logic and the study of automata theory. He created new methods to analyze finite automata, and had many contributions to the field of automata theory in algebra.

Moisil had important contributions in the creation of the first Romanian computers. He played a fundamental role in the development of computer science in Romania, and in raising the first generations of Romanian computer scientists. In 1996, he was awarded posthumously the *Computer Pioneer Award* by the Institute of Electrical and Electronics Engineers Computer Society.

## See also

- Boolean logic
- Jan Łukasiewicz

Łukasiewicz logic

- Ternary logic
- Lattices
- Multi-valued logic:

Łukasiewicz-Moisil algebras

- Quantum logic:

Quantum computers

- Algebraic logic:

MV-algebra

- Symbolic logic:

Mathematical logic

- Algebra
- Category theory:

Categorical logic, Adjoint functors

- Institute of Electrical and Electronics Engineers

## Notes

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- [2] <http://planetphysics.org/?op=getobj&from=books&id=253> Algebraic Mathematics and Logics. 2009., 400 pp, GNUL contributed book of 500+ contributing authors.
- [3] <http://planetphysics.org/encyclopedia/AlgebraicCategoryOfLMnLogicAlgebras.html> Algebraic category of  $LM_n$ -logic algebras
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- [7] <http://planetmath.org/?op=getobj&from=objects&id=10756> Quantum LM-algebraic Logic
- [8] <http://philpapers.org/autosense.pl?searchStr=George%20Georgescu> Web-generated list of Publications

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- International Conference on Computers, Communications & Control, ICCCC 2006 (<http://www.iccc.univagora.ro/iccc-2006/index.html>), at Agora University.
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- **(Romanian)** Simpozion "Spiritul moisilian pe meleaguri bihorene" ([http://www.univagora.ro/Arhiva/ArE2006/Simpozion\\_Moisil.html](http://www.univagora.ro/Arhiva/ArE2006/Simpozion_Moisil.html))
- **(Romanian)** MoisilBrasov.ro (<http://www.moisilbrasov.ro/>) - Colegiul National de Informatica "Grigore Moisil" Brasov
- **(Romanian)** LTGM.ro (<http://www.ltgm.ro/>) - Liceul Teoretic "Grigore Moisil" Urziceni

# Jan Łukasiewicz

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**Jan Łukasiewicz** (Polish pronunciation: [ˈjan wukaˈɫɛvʲit͡ɕ]) (21 December 1878 – 13 February 1956) was a Polish mathematician born in Lwów, Galicia, Austria-Hungary (now Lviv, Ukraine). His major mathematical work centred on mathematical logic. He thought innovatively about traditional propositional logic, the principle of non-contradiction and the law of excluded middle.

## Life and work

A number of axiomatizations of classical propositional logic are owed to Łukasiewicz. A particularly elegant axiomatization features a mere three axioms and is still invoked down to the present day. He was a pioneer investigator of multi-valued logics; his three-valued propositional calculus, introduced in 1917, was the first explicitly axiomatized non-classical logical calculus. He wrote on the philosophy of science. His approach to the making of scientific theories was similar to the thinking of Karl Popper.

Łukasiewicz invented the Polish notation (named after his nationality) for the logical connectives around 1920. This notation is the root of the idea of the *recursive stack*, a last-in, first-out computer memory store proposed by several researchers including Turing, Bauer and Hamblin, and first implemented in 1957. This design led to the English Electric multi-programmed KDF9 computer system of 1963, which had two such hardware register stacks. A similar concept underlies the reverse Polish notation (*RPN*, a postfix notation) of the Friden EC-130 calculator and its successors, many Hewlett Packard calculators, the Forth programming language, or the PostScript page description language.

At the beginning of World War II he worked at the secret Warsaw Underground University (Tajny Uniwersytet Warszawski), but by the end of the war he found refuge in Nazi Germany in the village of Hembsen, where he was brought for his own safety. Following the war he emigrated to Ireland and worked at the University of Dublin until his death.

## Chronology

- 1878 Born
  - 1890-1902 Studies with Kazimierz Twardowski in Lemberg (Lwów, L'viv)
  - 1902 Doctorate (mathematics and philosophy), University of Lemberg with the highest distinction possible
  - 1906 Habilitation thesis completed, University of Lemberg (Lwów, L'viv)
  - 1906 Becomes a lecturer
  - 1910 essays on the principle of non-contradiction and the excluded middle
  - 1911 extraordinary professor at Lemberg (Lwów, L'viv)
  - 1915 invited to the newly reopened University of Warsaw
  - 1916 new Kingdom of Poland declared
  - 1917 Develops three-valued propositional calculus
  - 1919 Polish Minister of Education
  - 1920–1939 professor at Warsaw University founds with Stanisław Leśniewski the Lwów-Warsaw School of logic (see also Alfred Tarski, Stefan Banach, Hugo Steinhaus, Zygmunt Janiszewski, Stefan Mazurkiewicz)
  - 1928 marries Regina Barwińska
  - 1944 flees to Germany and settles in Hembsen, where he was brought for his own safety.
  - 1946 exile in Belgium
  - 1946 offered a chair by the Royal Irish Academy
  - 1953 writes autobiography
  - 1956 Dies in Dublin
-

## See also

- Łukasiewicz logic
- History of philosophy in Poland
- Stanisław Leśniewski
- List of Poles
- 27114 Łukasiewicz

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# Notable cognitive scientists

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## Henry Stapp

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**Henry Stapp** is an American physicist, well-known for his work in quantum mechanics.

### Biography

After receiving his PhD in particle physics at the University of California, Berkeley, under the supervision of Nobel Laureates Emilio Segrè and Owen Chamberlain, Stapp moved to ETH Zurich to do post-doctoral work under Wolfgang Pauli. During this period he composed an article called 'Mind, Matter and Quantum Mechanics', which he never sent for publication, but would become the title of his 1993 book. When Pauli died in 1958, Stapp transferred to Munich, now in the company of Werner Heisenberg. While making important contributions to, inter alia, the analysis of proton-proton scattering and the development of analytic S-matrix theory, Stapp is perhaps most well known for his ongoing work in the foundations of quantum mechanics, with particular focus on explicating the role and nature of consciousness. He is also an expert on Bell's Theorem, having solved problems related to non-locality presented by John Bell and Albert Einstein.

He currently performs his research at the Lawrence Berkeley National Laboratory.

### Consciousness

Some of Stapp's work concerns the implications of quantum mechanics for consciousness.

Stapp sees a global collapse of superposed brain states as in the process of choosing between alternatives. Stapp points out that orthodox quantum theory reconciles two diverse aspects of scientific practice: the mathematical aspect represented by the deterministic evolution of mathematical properties in accordance with a deterministic equation Schrödinger's equation; and the empirical aspect associated with our human actions upon the world about us, and the feedbacks that we experience. Another way that he puts it is that the mathematically determined evolution via Schrödinger's equation is the 'rock like' aspect of matter, while the quantum collapse of the wave function is mind-like. His theory of how mind may interact with matter via quantum processes in the brain differs from that of Penrose and Hameroff. While the latter postulates quantum computing in the microtubules in brain neurons, Stapp postulates more global collapse via his 'mind like' wave-function collapse that exploits certain aspects of the quantum Zeno effect within the synapses to explain attention.

### Analysis

The known laws of quantum theory, taken as including wave function collapse, are indeterministic; they do not completely specify either the actions we take or the outcomes we experience in terms of the prior mathematical state of the universe, and the choice of action is not fixed even statistically. Thus, according to at least one orthodox contemporary theory, the universe of which we are parts evolves, insofar as contemporary science can say, in a way that need not be determined exclusively by the matter-like aspects of nature (although the existence of immaterial determining factors remains speculative). A corollary of this view of reality is that the history of the universe need not be a fixed 4 dimensional structure, as nineteenth century physics proclaimed, but is constantly forging ahead into the future, in keeping with common sense. According to Stapp, each increase in human knowledge is associated with a wave function collapse, which is an 'act of creation' that is a step along the arrow of time. Thus, free will could be seen as directly instrumental in the evolution of the universe.

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The emergence of Quantum Darwinism supports Stapp's theories of consciousness. Quantum Darwinism is a theory explaining the emergence of the classical world from the quantum world as due to a process of Darwinian selection. It is proposed by Wojciech Zurek and a group of collaborators including Ollivier, Poulin, Paz and Blume-Kohout. The development of the theory is due to the integration of a number of Zurek's research topics pursued over the course of twenty five years including: pointer states, einselection and decoherence.

## See also

- Quantum mind
- Consciousness causes collapse
- Quantum Zeno effect

## External links

- List of papers on LBNL server<sup>[1]</sup>

## References

[1] <http://www-physics.lbl.gov/~stapp/stappfiles.html>

# Karl H. Pribram



# Neuropsychology

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| <b>Mind and Brain Portal</b> |

**Karl H. Pribram** (born February 25, 1919 in Vienna, Austria) is a professor at Georgetown University , and an emeritus professor of psychology and psychiatry at Stanford University and Radford University. Board-certified as a neurosurgeon, Pribram did pioneering work on the definition of the limbic system, the relationship of the frontal cortex to the limbic system, the sensory-specific "association" cortex of the parietal and temporal lobes, and the classical motor cortex of the human brain. To the general public, Pribram is best known for his development of the holonomic brain model of cognitive function and his contribution to ongoing neurological research into memory, emotion, motivation and consciousness. American best selling author Katherine Neville is his significant other.

## Holonomic model

Pribram's holonomic model of brain processing states that, in addition to the circuitry accomplished by the large fiber tracts in the brain, processing also occurs in webs of fine fiber branches (for instance, dendrites) that form webs. This type of processing is properly described by Gabor quanta of information, wavelets that are used in quantum holography, the basis of fMRI, PET scans and other image processing procedures.

Gabor wavelets are windowed Fourier transforms that convert complex spatial (and temporal) patterns into component waves whose amplitudes at their intersections become reinforced or diminished. Fourier processes are the basis of holography. Holograms can correlate and store a huge amount of information - and have the advantage that the inverse transform returns the results of correlation into the spatial and temporal patterns that guide us in navigating our universe.

David Bohm had suggested that were we to view the cosmos without the lenses that outfit our telescopes, the universe would appear to us as a hologram. Pribram extended this insight by noting that were we deprived of the lenses of our eyes and the lens like processes of our other sensory receptors, we would be immersed in holographic experiences.

## Other contributions

In the late 1940s and early 1950s, Pribram's neurobehavioral experiments established the composition of the limbic system and the executive functions of the prefrontal cortex. Pribram also discovered the sensory specific systems of the association cortex, and showed that these systems operate to organize the choices we make among sensory stimuli, not the sensing of the stimuli themselves.

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## External links

- "The Holographic Brain" <sup>[4]</sup> - Dr. Jeffrey Mishlove interviews Karl Pribram
- "Comparison between Holographic Brain Theory and conventional models of neuronal computation" <sup>[5]</sup> – academic paper on Pribram's work
- "Pribram Receives Havel Prize For His Work in Neuroscience" <sup>[6]</sup> – news article
- Global Lens Interview <sup>[7]</sup> (Video)
- [38] quantum mind

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# David Chalmers

| David John Chalmers                                                               |                                                                                                           |
|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|
|  |                                                                                                           |
| <b>Full name</b>                                                                  | David John Chalmers                                                                                       |
| <b>Born</b>                                                                       | 20 April 1966<br>Australia                                                                                |
| <b>Era</b>                                                                        | Contemporary philosophy                                                                                   |
| <b>Region</b>                                                                     | Western Philosophy                                                                                        |
| <b>School</b>                                                                     | Analytic                                                                                                  |
| <b>Main interests</b>                                                             | Philosophy of mind<br>Consciousness                                                                       |
| <b>Notable ideas</b>                                                              | Hard problem of consciousness; property dualism; neutral monism; extended mind; two-dimensional semantics |

**David John Chalmers** (born 20 April 1966) is an Australian philosopher specializing in the area of philosophy of mind. He is Professor of Philosophy and Director of the Centre for Consciousness at the Australian National University.

## Background

Chalmers was born and raised in Australia, and since 2004 has been Professor of Philosophy, Director of the Centre for Consciousness, and an ARC Federation Fellow at the Australian National University. From an early age, he excelled at mathematics, eventually completing his undergraduate education at the University of Adelaide with a Bachelor's degree in mathematics and computer science. He then briefly studied at Lincoln College at the University of Oxford as a Rhodes Scholar before studying for his PhD at Indiana University Bloomington under Douglas Hofstadter. He was a postdoctoral fellow in the Philosophy-Neuroscience-Psychology program directed by Andy Clark at Washington University in St. Louis from 1993 to 1995, and his first professorship was at UC Santa Cruz, from August 1995 to December 1998. Chalmers was subsequently appointed Professor of Philosophy (1999-2004) and, later, Director of the Center for Consciousness Studies (2002-2004) at the University of Arizona, sponsor of the Toward a Science of Consciousness <sup>[1]</sup> conference where he made his legendary "debut" in 1994.

Chalmers' book, *The Conscious Mind* (1996), is widely considered (by both advocates and opponents) to be an essential work on consciousness and its relation to the mind-body problem in philosophy of mind.<sup>[2]</sup> In the book, Chalmers argues that all forms of physicalism (whether reductive or non-reductive) that have dominated modern philosophy and science fail to account for the existence (that is, presence in reality) of consciousness itself. He proposes an alternative dualistic view he calls *naturalistic dualism* (but which might also be characterized by more traditional formulations such as *property dualism*, *neutral monism*, or *double-aspect theory*). The book was described by *The Sunday Times* as "one of the best science books of the year".<sup>[3]</sup>

## Work

Chalmers is best known for his formulation of the notion of a hard problem of consciousness in both his book and in the paper "Facing Up to the Problem of Consciousness" (originally published in *The Journal of Consciousness Studies*, 1995). He makes the distinction between "easy" problems of consciousness, such as explaining object discrimination or verbal reports, and the single hard problem, which could be stated "why does the *feeling* which accompanies awareness of sensory information exist at all?" The essential difference between the (cognitive) easy problems and the (phenomenal) hard problem is that the former are at least theoretically answerable via the standard strategy in philosophy of mind: functionalism. Chalmers argues for an "explanatory gap" from the objective to the subjective, and criticizes physical explanations of mental experience, making him a dualist in an era that has been dominated by materialism.

In support of this, Chalmers is famous for his commitment to the logical (though, importantly, not physical) possibility of philosophical zombies, although he was not the first to propose the thought experiment. These zombies, unlike the zombie of popular fiction, are complete physical duplicates of human beings, lacking only qualitative experience. Chalmers argues that since such zombies are conceivable to us, they must therefore be logically possible. Since they are logically possible, then qualia and sentience are not fully explained by physical properties alone. Instead, Chalmers argues that consciousness is a fundamental property ontologically autonomous of any known (or even possible) physical properties, and that there may be lawlike rules which he terms "psychophysical laws" that determine which physical systems are associated with which types of qualia. However, he rejects Cartesian-style interactive dualism in which the mind has the power to alter the behavior of the brain, suggesting instead that the physical world is "causally closed" so that physical events only have physical causes, so that for example human *behavior* could be explained entirely in terms of the functions of the physical brain. He further speculates that all information-bearing systems may be conscious, leading him to entertain the possibility of conscious thermostats and a qualified panpsychism he calls panprotopsyism. Though Chalmers maintains a formal agnosticism on the issue, even conceding the viability of panpsychism places him at odds with the majority of his contemporaries.

After the publication of Chalmers' landmark paper, more than twenty papers in response were published in the *Journal of Consciousness Studies*. These papers (by Daniel Dennett, Colin McGinn, Francisco Varela, Francis Crick, and Roger Penrose among others) were collected and published in the book *Explaining Consciousness: The Hard Problem*. John Searle fiercely critiqued Chalmers's views in *The New York Review of Books*.<sup>[4]</sup>

Chalmers, with Andy Clark, has written *The Extended Mind*, an article about the borders of the mind<sup>[5]</sup>

## Miscellaneous

On his web site, David Chalmers has compiled a large bibliography on the philosophy of mind and related fields with close to 18000 annotated entries topically organized.

Chalmers appears in *The Matrix* video documentary "The Roots of the Matrix" and presents a novel take on a large part of the traditionally skeptical "brain in a vat" hypothesis. He maintains that this hypothesis is not, contrary to common philosophical opinion, a skeptical hypothesis.

He serves on the editorial board of the journals *Philo*, *Consciousness and Cognition*, the *Journal of Consciousness Studies*, and *Psyche*.

## Bibliography

A *partial* list of publications by Chalmers:

- *The Conscious Mind: In Search of a Fundamental Theory* (1996). Oxford University Press. hardcover: ISBN 0-19-511789-1, paperback: ISBN 0-19-510553-2
- *Toward a Science of Consciousness III: The Third Tucson Discussions and Debates* (1999). Stuart R. Hameroff, Alfred W. Kaszniak and David J. Chalmers (Editors). The MIT Press. ISBN 0-262-58181-7
- *Philosophy of Mind: Classical and Contemporary Readings* (2002). (Editor). Oxford University Press. ISBN 0-19-514581-X or ISBN 0-19-514580-1

## See also

- Hard problem of consciousness
- PhilPapers

## External links

- David Chalmers's web site <sup>[6]</sup>
- David Chalmers's bibliography <sup>[7]</sup>
- Fragments of Consciousness <sup>[8]</sup> - Chalmers's blog.
- Interview with Chalmers <sup>[9]</sup> - in Philosophy Now <sup>[10]</sup>.
- *Consciousness* <sup>[11]</sup>, an episode of Philosophy Talk, hosts Chalmers
- Video Interview <sup>[12]</sup> on BloggingHeads.tv by science writer John Horgan.
- The Mystery of Consciousness <sup>[13]</sup> on Bright SBM Production.

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- [2] <http://consc.net/book/reviews.html>
- [3] *The Conscious Mind: In Search of a Fundamental Theory* (1996), paperback edition, back cover.
- [4] Searle's review of *The Conscious Mind* ([http://www.nybooks.com/articles/article-preview?article\\_id=1258](http://www.nybooks.com/articles/article-preview?article_id=1258)) 6 March 1997 (subscription required)  
Chalmers' response to Searle and Searle's reply (<http://www.nybooks.com/articles/1179>) 15 May 1997 (free access)
- [5] <http://consc.net/papers/extended.html>.
- [6] <http://consc.net/chalmers/>
- [7] <http://consc.net/papers.html>
- [8] <http://fragments.consc.net/>
- [9] <http://www.philosophynow.org/issue21/21chalmers.htm>
- [10] <http://www.philosophynow.org>
- [11] <http://philosophytalk.org/pastShows/Consciousness.htm>
- [12] <http://bloggingheads.tv/diavlogs/254>
- [13] <http://brightsbm.com/interviews/index.php>

# George Gaylord Simpson

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| George Gaylord Simpson                                                            |                                                                                  |
|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
|  |                                                                                  |
| <b>Born</b>                                                                       | June 16, 1902                                                                    |
| <b>Died</b>                                                                       | October 6, 1984 (aged 82)                                                        |
| <b>Nationality</b>                                                                | American                                                                         |
| <b>Fields</b>                                                                     | Paleontology                                                                     |
| <b>Institutions</b>                                                               | Columbia University                                                              |
| <b>Known for</b>                                                                  | Modern synthesis; quantum evolution                                              |
| <b>Notable awards</b>                                                             | Linnean Society's Darwin-Wallace Medal 1958<br>Royal Society's Darwin Medal 1962 |

**George Gaylord Simpson** (16 June 1902 – 6 October 1984) was an American paleontologist. Simpson was perhaps the most influential paleontologist of the twentieth century, and a major participant in the modern evolutionary synthesis, contributing *Tempo and mode in evolution* (1944), *The meaning of evolution* (1949) and *The major features of evolution* (1953). He was an expert on extinct mammals and their intercontinental migrations. He anticipated such concepts as punctuated equilibrium (in *Tempo and mode*) and dispelled the myth that the evolution of the horse was a linear process culminating in the modern *Equus caballus*. He coined the word *hypodigm* in 1940, and published extensively on the taxonomy of fossil and extant mammals.<sup>[1]</sup>

He was Professor of Zoology at Columbia University, and Curator of the Department of Geology and Paleontology at the American Museum of Natural History from 1945 to 1959. He was Curator of the Museum of Comparative Zoology at Harvard University from 1959 to 1970, and a Professor of Geosciences at the University of Arizona until his retirement in 1982.

## Awards

He was awarded the Linnean Society of London's prestigious Darwin-Wallace Medal in 1958. He also received the Royal Society's Darwin Medal 'In recognition of his distinguished contributions to general evolutionary theory, based on a profound study of palaeontology, particularly of vertebrates,' in 1962.

At the University of Arizona, Tucson, the *Gould-Simpson Building* was named for George Gaylord Simpson.<sup>[2]</sup> Simpson was noted for his work in the field of paleogeography and continental evolution relationships.

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## Quotes

Man is the result of a purposeless and natural process that did not have him in mind.<sup>[3]</sup>

I don't think that evolution is supremely important because it is my specialty; it is my specialty because I think it is supremely important.<sup>[4]</sup>

## Books

- *Attending marvels* (1931)
- *Mammals and land bridges* (1940)
- *Tempo and mode in evolution* (1944)
- *The meaning of evolution* (1949)
- *Horses* (1951)
- *Evolution and geography* (1953)
- *The major features of evolution* (1953)
- *Life: an introduction to biology* (1957)
- *Principles of animal taxonomy* (1961)
- *This view of life* (1964)
- *The geography of evolution* (1965)
- *Penguins* (1976)
- *Concession to the improbable* (1978) (an autobiography)
- *Splendid isolation* (1980)
- *The Dechronization of Sam Magruder* (posthumously published novella, 1996)

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  - [2] Gould-Simpson Building, Univ. of Arizona (<http://iiewww.ccit.arizona.edu/uamap/staticLarge/77.html>)
  - [3] George Gaylord Simpson, *The Meaning of Evolution*, revised edition (New Haven: Yale University Press, 1967), p. 345.
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- Gershenowitz, H (1978), "George Gaylord Simpson and Lamarck.", *Indian journal of history of science* **13** (1): 56–61, PMID 11615952 (<http://www.ncbi.nlm.nih.gov/pubmed/11615952>)

## External links

- George Gaylord Simpson (<http://people.ucsc.edu/~laporte/simpson/Index.html>) — full and comprehensive biography by L. F. Laporte
- George Gaylord Simpson ([http://www.stephenjaygould.org/people/george\\_simpson.html](http://www.stephenjaygould.org/people/george_simpson.html)) — biographical sketch from The Stephen Jay Gould Archive
- George Gaylord Simpson ([http://www.pbs.org/wgbh/evolution/library/06/2/1\\_062\\_02.html](http://www.pbs.org/wgbh/evolution/library/06/2/1_062_02.html)) — a short biography from the PBS *Evolution* website
- George Gaylord Simpson Papers, American Philosophical Society. (<http://www.amphilsoc.org/library/mole/s/simpson.htm>)

## See also

- Annie Montague Alexander, who helped finance some of his early work

# Theoretical Biophysics

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**Biophysics** is an interdisciplinary science that uses the methods of physics and physical chemistry to study biological systems.<sup>[1]</sup> Studies included under the branches of biophysics span all levels of biological organization, from the molecular scale to whole organisms and ecosystems. Biophysical research shares significant overlap with biochemistry, nanotechnology, bioengineering, agrophysics and systems biology.

Molecular biophysics typically addresses biological questions that are similar to those in biochemistry and molecular biology, but the questions are approached quantitatively. Scientists in this field conduct research concerned with understanding the interactions between the various systems of a cell, including the interactions between DNA, RNA and protein biosynthesis, as well as how these interactions are regulated. A great variety of techniques are used to answer these questions.

Fluorescent imaging techniques, as well as electron microscopy, x-ray crystallography, NMR spectroscopy and atomic force microscopy (AFM) are often used to visualize structures of biological significance. Conformational change in structure can be measured using techniques such as dual polarisation interferometry and circular dichroism. Direct manipulation of molecules using optical tweezers or AFM can also be used to monitor biological events where forces and distances are at the nanoscale. Molecular biophysicists often consider complex biological events as systems of interacting units which can be understood through statistical mechanics, thermodynamics and chemical kinetics. By drawing knowledge and experimental techniques from a wide variety of disciplines, biophysicists are often able to directly observe, model or even manipulate the structures and interactions of individual molecules or complexes of molecules.

In addition to traditional (i.e. molecular and cellular) biophysical topics like structural biology or enzyme kinetics, modern biophysics encompasses an extraordinarily broad range of research. It is becoming increasingly common for biophysicists to apply the models and experimental techniques derived from physics, as well as mathematics and statistics, to larger systems such as tissues, organs, populations and ecosystems.

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## Focus as a subfield

Biophysics often does not have university-level departments of its own, but has presence as groups across departments within the fields of molecular biology, biochemistry, chemistry, computer science, mathematics, medicine, pharmacology, physiology, physics, and neuroscience. What follows is a list of examples of how each department applies its efforts toward the study of biophysics. This list is hardly all inclusive. Nor does each subject of study belong exclusively to any particular department. Each academic institution makes its own rules and there is much overlap between departments.

- Biology and molecular biology - Almost all forms of biophysics efforts are included in some biology department somewhere. To include some: gene regulation, single protein dynamics, bioenergetics, patch clamping, biomechanics.
- Structural biology - Ångstrom-resolution structures of proteins, nucleic acids, lipids, carbohydrates, and complexes thereof.
- Biochemistry and chemistry - biomolecular structure, siRNA, nucleic acid structure, structure-activity relationships.
- Computer science - Neural networks, biomolecular and drug databases.
- Computational chemistry - molecular dynamics simulation, molecular docking, quantum chemistry
- Bioinformatics - sequence alignment, structural alignment, protein structure prediction
- Mathematics - graph/network theory, population modeling, dynamical systems, phylogenetics.
- Medicine and neuroscience - tackling neural networks experimentally (brain slicing) as well as theoretically (computer models), membrane permittivity, gene therapy, understanding tumors.
- Pharmacology and physiology - channel biology, biomolecular interactions, cellular membranes, polyketides.
- Physics - biomolecular free energy, stochastic processes, covering dynamics.
- Quantum Biophysics involves quantum information processing of coherent states, entanglement between coherent protons and transcriptase components and replication of decohered isomers to yield time-dependent base substitutions. These studies imply applications in quantum computing.
- Agronomy Agriculture

Many biophysical techniques are unique to this field. Research efforts in biophysics are often initiated by scientists who were traditional physicists, chemists, and biologists by training.

## See also

- List of biophysics topics
  - List of biophysicists
  - Biophysical chemistry
  - Medical biophysics
  - Membrane biophysics
  - Molecular biophysics
  - Important publications in biophysics
-

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## External links

- Biophysical Society <sup>[4]</sup>
- Educational Resources from Biophysical Society <sup>[5]</sup>
- The European Biophysical Societies Association <sup>[6]</sup>
- The Wellcome Trust Physiome Project <sup>[7]</sup> - Links
- Nasif Nahle, Biophysics <sup>[8]</sup>

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- [3] <http://personalwebs.oakland.edu/~roth/hobbie.htm>
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- [6] <http://www.ebsa.org/>
- [7] <http://www.physiome.ox.ac.uk/>
- [8] <http://biocab.org/Biophysics.html>

# Theoretical biology

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**Theoretical biology** is a field of academic study and research that involves the use of models and theories in biology.

Initial scientific efforts to understand complex biological phenomena, such as evolution by natural selection or human consciousness, can be described as theoretical "framework" approaches. The common use of this word throughout the biological literature has only recently culminated in a formal definition offered by Francis Crick and Christof Koch:

"A framework is not a detailed hypothesis or set of hypotheses; rather, it is a suggested point of view for an attack on a scientific problem, often suggesting testable hypotheses. Biological frameworks differ from frameworks in physics and chemistry because of the nature of evolution. Biological systems do not have rigid laws, as physics has. Evolution produces mechanisms, and often submechanisms, so that there are few "rules" in biology which do not have occasional exceptions.

A good framework is one that sounds reasonably plausible relative to available scientific data and that turns out to be largely correct. It is unlikely to be correct in all the details. A framework often contains unstated (and often unrecognized) assumptions, but this is unavoidable."<sup>[1]</sup>

Such evidence-based logical frameworks serve to motivate both experimental and further theoretical refinement, and the formulation of testable hypotheses. For example, the synchronization of senescence by natural selection, a concept central to the prevailing evolutionary view of senescence and initially advanced by George C. Williams in 1957<sup>[2]</sup> and later extended and refined by John Maynard Smith<sup>[3]</sup> has been described as a framework in agreement with Crick and Koch's definition<sup>[4] [5]</sup>. Their definition has been used explicitly in attempts to understand anorexia nervosa<sup>[6]</sup> and to understand and formulate treatment options for obesity<sup>[7]</sup>.

The absence, paucity or dispensability of mathematics in important theoretical biological frameworks such as those cited above, and indeed in the foundational work of many evolutionary theorists including Charles Darwin, are existence proofs that theoretical biology is somewhat distinct from mathematical or computational biology. Nevertheless, the ultimate goal of the theoretical biologist is to explain the biological world using mainly mathematical and computational tools. Though it is ultimately based on observations and experimental results, the theoretical biologist's product is a model or theory, and it is this that chiefly distinguishes the theoretical biologist from other biologists.

Many separate areas of biology fall under the concept of theoretical biology, according to the way they are studied. Some of these areas include: animal behaviour (ethology), biomechanics, biorhythms, cell biology, complexity of biological systems, ecology, enzyme kinetics, evolutionary biology, genetics, immunology, membrane transport, microbiology, molecular structures, morphogenesis, physiological mechanisms, systems biology and the origin of life. Neurobiology is an example of a subdiscipline of biology which already has a theoretical version of its own, theoretical or computational neuroscience.

## Theoretical biologists

- Ervin Bauer
  - Ludwig von Bertalanffy
  - Francis Crick
  - Charles Darwin
  - Richard Dawkins
  - Walter M. Elsasser
  - Claus Emmeche
  - Ronald A. Fisher
  - Brian Goodwin
  - J. B. S. Haldane
  - William D. Hamilton
  - Lionel G. Harrison
  - Michael Hassell
  - Sven Erik Jørgensen
  - George Karreman
  - Stuart Kauffman
  - Christof Koch
  - Kalevi Kull
  - Simon Levin
  - Richard Lewontin
  - Humberto Maturana
  - Robert May
  - John Maynard Smith
  - Gerd B. Müller
  - George R. Price
  - Erik Rauch
  - Nicolas Rashevsky
  - Ronald Brown (mathematician)
  - Johannes Reinke
  - Robert Rosen
  - Peter Schuster
  - George Sugihara
  - René Thom
  - D'Arcy Thompson
  - Robert Trivers
  - Jakob von Uexküll
  - Robert Ulanowicz
  - Francisco Varela
  - C. H. Waddington
  - George C. Williams
  - E. O. Wilson
  - Arthur Winfree
  - Lewis Wolpert
  - Sewall Wright
-

## See also

- Journal of Theoretical Biology
- Bioinformatics
- Biosemiotics
- Mathematical biology
- Theoretical ecology
- Artificial life

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## External links

- Theory of Biological Anthropology (Documents No. 9 and 10 in English) <sup>[8]</sup>
- Drawing the Line Between Theoretical and Basic Biology (a forum article by Isidro T. Savillo) <sup>[9]</sup>

## Related Journals

- Acta Biotheoretica <sup>[10]</sup>
- Bioinformatics <sup>[11]</sup>
- Biological Theory <sup>[12]</sup>
- BioSystems <sup>[13]</sup>
- Bulletin of Mathematical Biology <sup>[14]</sup>
- Ecological Modelling <sup>[15]</sup>
- Journal of Mathematical Biology <sup>[16]</sup>
- Journal of Theoretical Biology <sup>[17]</sup>
- Journal of the Royal Society Interface <sup>[18]</sup>
- Mathematical Biosciences <sup>[19]</sup>
- Medical Hypotheses <sup>[20]</sup>
- Rivista di Biologia-Biology Forum <sup>[21]</sup>
- Theoretical and Applied Genetics <sup>[22]</sup>
- Theoretical Biology and Medical Modelling <sup>[23]</sup>
- Theoretical Population Biology <sup>[24]</sup>
- Theory in Biosciences <sup>[25]</sup> (formerly: Biologisches Zentralblatt)

## Related societies

- ESMTB: European Society for Mathematical and Theoretical Biology <sup>[26]</sup>
- The Israeli Society for Theoretical and Mathematical Biology <sup>[27]</sup>
- Société Francophone de Biologie Théorique <sup>[28]</sup>
- International Society for Biosemiotic Studies <sup>[29]</sup>

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- [24] <http://www.elsevier.com/locate/issn/00405809>
- [25] [http://www.elsevier.com/wps/product/cws\\_home/701802](http://www.elsevier.com/wps/product/cws_home/701802)
- [26] <http://www.esmtb.org/>
- [27] <http://bioinformatics.weizmann.ac.il/istmb/>
- [28] <http://www.necker.fr/sfbt/>
- [29] <http://www.biosemiotics.org/>

# Biocybernetics

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**Biocybernetics** is the application of cybernetics to biological science, composed of biological disciplines that benefit from the application of cybernetics: neurology, multicellular systems and others. Biocybernetics plays a major role in systems biology, seeking to integrate different levels of information to understand how biological systems function.

Biocybernetics as an abstract science is a part of theoretical biology, and based upon the principles of systemics.

## Terminology

Biocybernetics is a cojoined word from bio (Greek: βίο / life) and cybernetics (Greek: κυβερνητική / controlling-governing). It is sometimes written together or with a blank or written fully as biological cybernetics, whilst the same rules apply. Most write it together though, as Google statistics show. The same applies to neuro cybernetics which should also be looked up as neurological, when doing extensive research.

## Same or familiar fields

As those disciplines are dealing on theoretical/abstract foundations and are in accordance with the popularity of computers. Thus papers and research is in greater numbers going on under different names: e.g. molecular cybernetics -> molecular computational systems OR molecular systems theory OR molecular systemics OR molecular information/informational systems

Please heed this when you engage in an extensive search for information to assure access to a broad range of papers.

## Categories

- biocybernetics - the study of an entire living organism
- neurocybernetics - cybernetics dealing with neurological models. (psycho-cybernetics was the title of a self-help book, and is not a scientific discipline)
- molecular cybernetics - cybernetics dealing with molecular systems (e.g. molecular biology cybernetics)
- cellular cybernetics - cybernetics dealing with cellular systems (e.g. information technology/cell phones,... or biological cells)
- evolutionary cybernetics - study of the evolution of informational systems (See also evolutionary programming, evolutionary algorithm)
- any distinct informational system within the realm of biology

## See also

- Bioinformatics
  - Biosemiotics
  - Computational biology
  - Computational biomodeling
  - Medical cybernetics
-



## External links

- Journal "Biological Cybernetics" <sup>[1]</sup>
- Scientific portal on biological cybernetics <sup>[2]</sup>
- UCLA Biocybernetics Laboratory <sup>[3]</sup>

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# Mathematical sociology

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**Mathematical sociology** is the usage of mathematics to construct social theories. In sociology, in general, the connection between mathematics and sociology is confined to problems of data analysis; employing statistical models. Many sociological theories are strong in intuitive content, but weak from a formal point of view. In mathematical sociology, the preferred style is encapsulated in the phrase "constructing a mathematical model." This means making specified assumptions about some mathematical objects and providing an empirical interpretation for the ideas. It also means deducing properties of the model and comparing these with relevant empirical data.

## History

Starting in the early 1940s, Nicolas Rashevsky<sup>[1] [2]</sup>, and subsequently in the late 1940s, Anatol Rapoport and others, developed a relational and probabilistic approach to the characterization of large social networks in which the nodes are persons and the links are acquaintanceship. During late 1940s, formulas were derived that connected local parameters such as closure of contacts – if A is linked to both B and C, then there is a greater than chance probability that B and C are linked to each other – to the global network property of connectivity<sup>[3]</sup>.

Moreover, acquaintanceship is a *positive tie*, but what about *negative ties* such as animosity among persons? To tackle this problem, graph theory, which is the mathematical study of abstract representations of networks of points and lines, can be extended to include these two types of links and thereby to create models that represent both positive and negative sentiment relations, which are represented as signed graphs. A signed graph is called *balanced* if the product of the signs of all relations in every cycle (links in every graph cycle) is positive. This effort led to Harary's Structure Theorem (1953), which says that if a network of interrelated positive and negative ties is balanced, e.g. as illustrated by the psychological principle that "my friend's enemy is my enemy", then it consists of two subnetworks such that each has positive ties among its nodes and there are only negative ties between nodes in distinct subnetworks.<sup>[4]</sup> The imagery here is of a social system that splits into two cliques. There is, however, a special case where one of the two subnetworks is empty, which might occur in very small networks.

In another model, ties have relative strengths. 'Acquaintanceship' can be viewed as a 'weak' tie and 'friendship' is represented as a strong tie. Like its uniform cousin discussed above, there is a concept of closure, called strong triadic closure. A graph satisfies strong triadic closure If A is strongly connected to B, and B is strongly connected to C, then A and C must have a tie (either weak or strong).

In these two developments we have mathematical models bearing upon the analysis of structure. Other early influential developments in mathematical sociology pertained to process. For instance, in 1952 Herbert Simon produced a mathematical formalization of a published theory of social groups by constructing a model consisting of a deterministic system of differential equations. A formal study of the system led to theorems about the dynamics and the implied equilibrium states of any group.

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## Further developments

The model constructed by Simon raises a question: how can one connect such theoretical models to the data of sociology, which often take the form of surveys in which the results are expressed in the form of proportions of people believing or doing something. This suggests deriving the equations from assumptions about the chances of an individual changing state in a small interval of time, a procedure well known in the mathematics of stochastic processes.

Sociologist, James S. Coleman embodied this idea in his 1964 book *Introduction to Mathematical Sociology*, which showed how stochastic processes in social networks could be analyzed in such a way as to enable testing of the constructed model by comparison with the relevant data. In addition, Coleman employed mathematical ideas drawn from economics, such as general equilibrium theory, to argue that general social theory should begin with a concept of purposive action and, for analytical reasons, approximate such action by the use of rational choice models (Coleman, 1990). This argument provided impetus for the emergence of a good deal of effort to link rational choice thinking to more traditional sociological concerns involving social structures.

Meanwhile, structural analysis of the type indicated earlier received a further extension to social networks based on institutionalized social relations, notably those of kinship. The linkage of mathematics and sociology here involved abstract algebra, in particular, group theory<sup>[5]</sup>. This, in turn, led to a focus on a data-analytical version of homomorphic reduction of a complex social network (which along with many other techniques is presented in Wasserman and Faust 1994<sup>[6]</sup>).

Some programs of research in sociology employ experimental methods to study social interaction processes. Joseph Berger and his colleagues initiated such a program in which the central idea is the use of the theoretical concept "expectation state" to construct theoretical models to explain interpersonal processes, e.g., those linking external status in society to differential influence in local group decision-making. Much of this theoretical work is linked to mathematical model building (Berger 2000).

The generations of mathematical sociologists that followed Rapoport, Simon, Harary, Coleman, White and Berger, including those entering the field in the 1960s such as Thomas Fararo, Philip Bonacich, and Tom Mayer, among others, drew upon their work in a variety of ways.

## Texts and journals

Mathematical sociology textbooks cover a variety of models, usually explaining the required mathematical background before discussing important work in the literature (Fararo 1973, Leik and Meeker 1975). The *Journal of Mathematical Sociology* (started in 1971) has been open to papers covering a broad spectrum of topics employing a variety of types of mathematics, especially through frequent special issues. Articles in *Social Networks*, a journal devoted to social structural analysis, very often employ mathematical models and related structural data analyses. In addition, and this is important as an indicator of the penetration of mathematical model building into sociological research, the major comprehensive journals in sociology, especially *The American Journal of Sociology* and *The American Sociological Review*, regularly publish articles featuring mathematical formulations.

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## See also

- Positivism
- Statistics
- Computational sociology
- Harrison White
- Nicolas Rashevsky
- Society for Mathematical Biology
- Interpersonal ties
- Duncan Watts
- James Samuel Coleman
- James D. Montgomery
- Thomas Fararo
- Social network

## External links

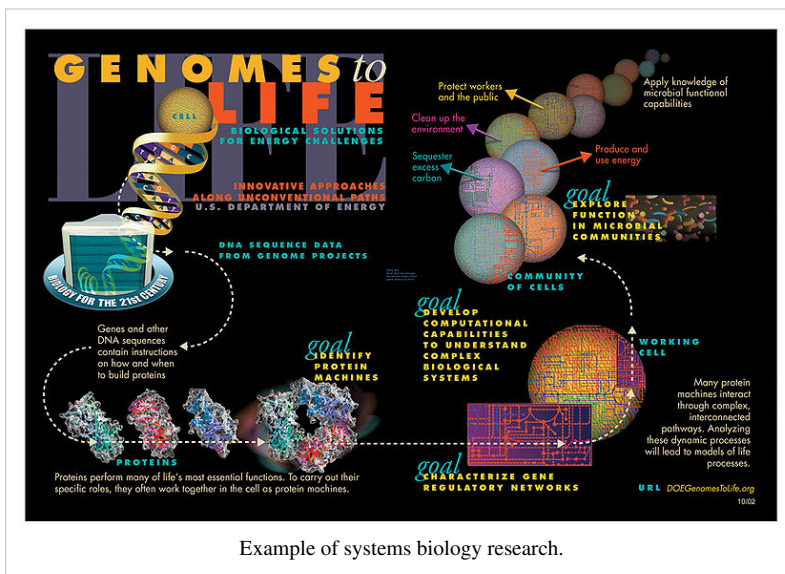
- Mathematical Sociology Section Home Page <sup>[7]</sup>
- Mathematical Sociology <sup>[8]</sup> - an indepth explanation by Phil Bonacich
- *The Society for Mathematical Biology* <sup>[13]</sup>
- Bulletin of Mathematical Biophysics <sup>[6]</sup>
- European Society for Mathematical and Theoretical Biology (ESMTB) <sup>[9]</sup>

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- [8] <http://www.sscnet.ucla.edu/soc/faculty/bonacich/textbook.htm>
- [9] <http://www.esmtb.org/news/news.htm>

## Complex Systems biology

**Systems biology** is a term used to describe a number of trends in bioscience research, and a movement which draws on those trends. Proponents describe systems biology as a biology-based inter-disciplinary study field that focuses on complex interactions in biological systems, claiming that it uses a new perspective (holism instead of reduction). Particularly from year 2000 onwards, the term is used widely in the biosciences, and in a variety of contexts. An often stated ambition of systems biology is the modeling and discovery of emergent properties, properties of a system whose theoretical description is only possible using techniques which fall under the remit of systems biology.



Example of systems biology research.

## Overview

Systems biology can be considered from a number of different aspects:

- As a **field of study**, particularly, the study of the interactions between the components of *biological systems*, and how these interactions give rise to the function and behavior of that system (for example, the enzymes and metabolites in a metabolic pathway).<sup>[1] [2]</sup>
- As a **paradigm**, usually defined in antithesis to the so-called reductionist paradigm (biological organisation), although fully consistent with the scientific method. The distinction between the two paradigms is referred to in these quotations:

*"The reductionist approach has successfully identified most of the components and many of the interactions but, unfortunately, offers no convincing concepts or methods to understand how system properties emerge...the pluralism of causes and effects in biological networks is better addressed by observing, through quantitative measures, multiple components simultaneously and by rigorous data integration with mathematical models"* Science<sup>[3]</sup>

*"Systems biology...is about putting together rather than taking apart, integration rather than reduction. It requires that we develop ways of thinking about integration that are as rigorous as our reductionist programmes, but different....It means changing our philosophy, in the full sense of the term"* Denis Noble<sup>[4]</sup>

- As a series **operational protocols used for performing research**, namely a cycle composed of theory, analytic or computational modelling to propose specific testable hypotheses about a biological system, experimental validation, and then using the newly acquired quantitative description of cells or cell processes to refine the computational model or theory.<sup>[5] [6]</sup> Since the objective is a model of the interactions in a system, the experimental techniques that most suit systems biology are those that are system-wide and attempt to be as complete as possible. Therefore, transcriptomics, metabolomics, proteomics and high-throughput techniques are used to collect quantitative data for the construction and validation of models.
- As the application of dynamical systems theory to molecular biology.
- As a **socioscientific phenomenon** defined by the strategy of pursuing integration of complex data about the interactions in biological systems from diverse experimental sources using interdisciplinary tools and personnel.

This variety of viewpoints is illustrative of the fact that systems biology refers to a cluster of peripherally overlapping concepts rather than a single well-delineated field. However the term has widespread currency and popularity as of 2007, with chairs and institutes of systems biology proliferating worldwide (Such as the Institute for Systems Biology).

## History

Systems biology finds its roots in:

- the quantitative modeling of enzyme kinetics, a discipline that flourished between 1900 and 1970,
- the mathematical modeling of population growth,
- the simulations developed to study neurophysiology, and
- control theory and cybernetics.

One of the theorists who can be seen as a precursor of systems biology is Ludwig von Bertalanffy with his general systems theory, "organism biology" (he defined "organism" as the concept of "system") and his book titled "General Systems Theory in Physics and Biology" was published in 1950. One of the first numerical simulations in biology was published in 1952 by the British neurophysiologists and Nobel prize winners Alan Lloyd Hodgkin and Andrew Fielding Huxley, who constructed a mathematical model that explained the action potential propagating along the axon of a neuronal cell.<sup>[7]</sup> Their model described a cellular function emerging from the interaction between two different molecular components, a potassium and a sodium channels, and can therefore be seen as the beginning of

computational systems biology.<sup>[8]</sup> In 1960, Denis Noble developed the first computer model of the heart pacemaker.<sup>[9]</sup>

The formal study of systems biology, as a distinct discipline, was launched by systems theorist Mihajlo Mesarovic in 1966 with an international symposium at the Case Institute of Technology in Cleveland, Ohio entitled "Systems Theory and Biology."<sup>[10] [11]</sup>

The 1960s and 1970s saw the development of several approaches to study complex molecular systems, such as the Metabolic Control Analysis and the biochemical systems theory. The successes of molecular biology throughout the 1980s, coupled with a skepticism toward theoretical biology, that then promised more than it achieved, caused the quantitative modelling of biological processes to become a somewhat minor field.

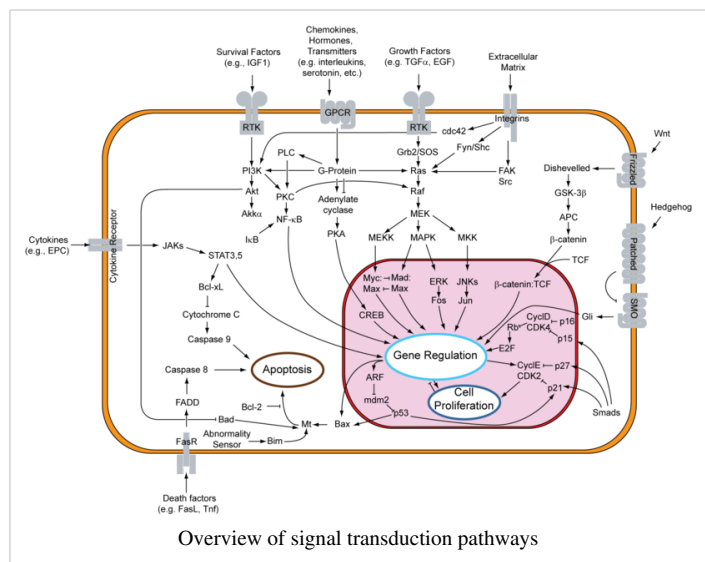
However the birth of functional genomics in the 1990s meant that large quantities of high quality data became available, while the computing power exploded, making more realistic models possible. In 1997, the group of Masaru Tomita published the first quantitative model of the metabolism of a whole (hypothetical) cell. The term of "systems biology" can be found in the article of Zieglansberger W. and Tolle TR, 1993 (Pub-Med, NIH). During the 1990s years, Zeng B.J. created the concept, model and terms of "system medicine" (April, 1992), "system bio-engineering" (June, 1994) and "systems genetics"(Nov. 1994)" in China, and established the Associates for Biosystem Science and Engineering in 1999, Germany.

Around the year 2000, when Institutes of Systems Biology were established in Seattle and Tokyo, systems biology emerged as a movement in its own right, spurred on by the completion of various genome projects, the large increase in data from the omics (e.g. genomics and proteomics) and the accompanying advances in high-throughput experiments and bioinformatics. Since then, various research institutes dedicated to systems biology have been developed. As of summer 2006, due to a shortage of people in systems biology<sup>[12]</sup> several doctoral training centres in systems biology have been established in many parts of the world.

## Techniques associated with systems biology

According to the interpretation of System Biology as the ability to obtain, integrate and analyze complex data from multiple experimental sources using interdisciplinary tools, some typical technology platforms are:

- **Genomics:** Organismal deoxyribonucleic acid(DNA) sequence, including intra-organisamal cell specific variation. (i.e. Telomere length variation etc).
- **Epigenomics / Epigenetics:** Organismal and corresponding cell specific transcriptomic regulating factors not empirically coded in the genomic sequence. (i.e. DNA methylation, Histone Acetelation etc).
- **Transcriptomics:** Organismal, tissue or whole cell gene expression measurements by DNA microarrays or serial analysis of gene expression
- **Interferomics:** Organismal, tissue, or cell level transcript correcting factors (i.e. RNA interference)
- **Translatomics / Proteomics:** Organismal, tissue, or cell level measurements of proteins and peptides via two-dimensional gel electrophoresis, mass spectrometry or multi-dimensional protein identification techniques (advanced HPLC systems coupled with mass spectrometry). Sub disciplines include phosphoproteomics, glycoproteomics and other methods to detect chemically modified proteins.



- **Metabolomics:** Organismal, tissue, or cell level measurements of all small-molecules known as metabolites.
- **Glycomics:** Organismal, tissue, or cell level measurements of carbohydrates.
- **Lipidomics:** Organismal, tissue, or cell level measurements of lipids.

In addition to the identification and quantification of the above given molecules further techniques analyze the dynamics and interactions within a cell. This includes:

- **Interactomics:** Organismal, tissue, or cell level study of interactions between molecules. Currently the authoritative molecular discipline in this field of study is protein-protein interactions (PPI), although the working definition does not pre-clude inclusion of other molecular disciplines such as those defined here.
- **Fluxomics:** Organismal, tissue, or cell level measurements of molecular dynamic changes over time.
- **Biomics:** systems analysis of the biome.

The investigations are frequently combined with large scale perturbation methods, including gene-based (RNAi, mis-expression of wild type and mutant genes) and chemical approaches using small molecule libraries. Robots and automated sensors enable such large-scale experimentation and data acquisition. These technologies are still emerging and many face problems that the larger the quantity of data produced, the lower the quality. A wide variety of quantitative scientists (computational biologists, statisticians, mathematicians, computer scientists, engineers, and physicists) are working to improve the quality of these approaches and to create, refine, and retest the models to accurately reflect observations.

The systems biology approach often involves the development of mechanistic models, such as the reconstruction of dynamic systems from the quantitative properties of their elementary building blocks.<sup>[13] [14]</sup> For instance, a cellular network can be modelled mathematically using methods coming from chemical kinetics and control theory. Due to the large number of parameters, variables and constraints in cellular networks, numerical and computational techniques are often used. Other aspects of computer science and informatics are also used in systems biology. These include new forms of computational model, such as the use of process calculi to model biological processes, the integration of information from the literature, using techniques of information extraction and text mining, the development of online databases and repositories for sharing data and models (such as BioModels Database), approaches to database integration and software interoperability via loose coupling of software, websites and databases such as Gaggle<sup>[15]</sup>, SBW<sup>[16]</sup>, or commercial suits, and the development of syntactically and semantically sound ways of representing biological models, such as the Systems Biology Markup Language (SBML).

## See also

### Related fields

- Complex systems
- Complex systems biology
- Bioinformatics
- Biological network inference
- Biological systems engineering
- Biomedical cybernetics
- Biostatistics
- Extrapolation based molecular systems biology
- Theoretical Biophysics
- Relational Biology
- Translational Research
- Computational biology
- Computational systems biology
- Scotobiology
- Synthetic biology
- Systems biology modeling
- Systems ecology
- Systems immunology

### Related terms

- Life
- Biological organisation
- Artificial life
- Gene regulatory network
- Metabolic network modelling
- Living systems theory
- Network Theory of Aging
- Regulome
- Systems Biology Markup Language (SBML)
- SBO
- Viable System Model
- Antireductionism

### Systems biologists

- Category:Systems biologists

### Lists

- Category:Systems biologists
- List of systems biology conferences
- List of omics topics in biology
- List of publications in systems biology
- List of systems biology research groups

## Further reading

### Books

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### Journals

- BMC Systems Biology <sup>[21]</sup> - open access journal on systems biology
- Molecular Systems Biology <sup>[22]</sup> - open access journal on systems biology
- IET Systems Biology <sup>[23]</sup> - not open access journal on systems biology
- WIREs Systems Biology and Medicine <sup>[24]</sup> - open access journal on systems biology and medicine

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## External links

- Applied BioDynamics Laboratory: Boston University<sup>[44]</sup>
- Systems Biology - BioChemWeb.org<sup>[45]</sup>
- Systems Biology Portal<sup>[46]</sup> - administered by the Systems Biology Institute
- Semantic Systems Biology<sup>[47]</sup>
- SystemsX.ch<sup>[48]</sup> - The Swiss Initiative in Systems Biology
- Systems Biology at the Pacific Northwest National Laboratory<sup>[49]</sup>

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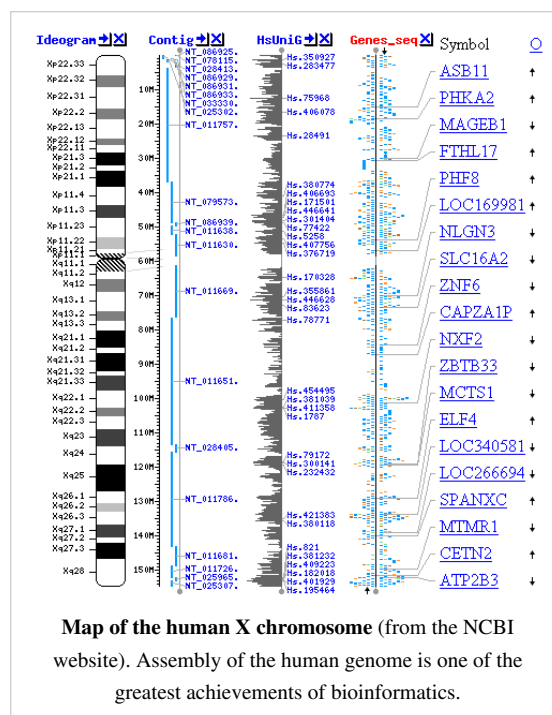
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## Bioinformatics

**Bioinformatics** is the application of information technology and computer science to the field of molecular biology. The term *bioinformatics* was coined by Paulien Hogeweg in 1979 for the study of informatic processes in biotic systems. Its primary use since at least the late 1980s has been in genomics and genetics, particularly in those areas of genomics involving large-scale DNA sequencing. Bioinformatics now entails the creation and advancement of databases, algorithms, computational and statistical techniques, and theory to solve formal and practical problems arising from the management and analysis of biological data. Over the past few decades rapid developments in genomic and other molecular research technologies and developments in information technologies have combined to produce a tremendous amount of information related to molecular biology. It is the name given to these mathematical and computing approaches used to glean understanding of biological processes. Common activities in bioinformatics include mapping and analyzing DNA and protein sequences, aligning different DNA and protein sequences to compare them and creating and viewing 3-D models of protein structures.

The primary goal of bioinformatics is to increase our understanding of biological processes. What sets it apart from other approaches, however, is its focus on developing and applying computationally intensive techniques (e.g., pattern recognition, data mining, machine learning algorithms, and visualization) to achieve this goal. Major research efforts in the field include sequence alignment, gene finding, genome assembly, protein structure alignment, protein structure prediction, prediction of gene expression and protein-protein interactions, genome-wide association studies and the modeling of evolution.



## Introduction

Bioinformatics was applied in the creation and maintenance of a database to store biological information at the beginning of the "genomic revolution", such as nucleotide and amino acid sequences. Development of this type of database involved not only design issues but the development of complex interfaces whereby researchers could both access existing data as well as submit new or revised data.

In order to study how normal cellular activities are altered in different disease states, the biological data must be combined to form a comprehensive picture of these activities. Therefore, the field of bioinformatics has evolved such that the most pressing task now involves the analysis and interpretation of various types of data, including nucleotide and amino acid sequences, protein domains, and protein structures. The actual process of analyzing and interpreting data is referred to as computational biology. Important sub-disciplines within bioinformatics and computational biology include:

**a)** the development and implementation of tools that enable efficient access to, and use and management of, various types of information. **b)** the development of new algorithms (mathematical formulas) and statistics with which to assess relationships among members of large data sets, such as methods to locate a gene within a sequence, predict protein structure and/or function, and cluster protein sequences into families of related sequences.

## Major research areas

### Sequence analysis

Since the Phage  $\Phi$ -X174 was sequenced in 1977, the DNA sequences of thousands of organisms have been decoded and stored in databases. This sequence information is analyzed to determine genes that encode polypeptides (proteins), RNA genes, regulatory sequences, structural motifs, and repetitive sequences. A comparison of genes within a species or between different species can show similarities between protein functions, or relations between species (the use of molecular systematics to construct phylogenetic trees). With the growing amount of data, it long ago became impractical to analyze DNA sequences manually. Today, computer programs such as BLAST are used daily to search the genomes of thousands of organisms, containing billions of nucleotides. These programs can compensate for mutations (exchanged, deleted or inserted bases) in the DNA sequence, in order to identify sequences that are related, but not identical. A variant of this sequence alignment is used in the sequencing process itself. The so-called shotgun sequencing technique (which was used, for example, by The Institute for Genomic Research to sequence the first bacterial genome, *Haemophilus influenzae*) does not produce entire chromosomes, but instead generates the sequences of many thousands of small DNA fragments (ranging from 35 to 900 nucleotides long, depending on the sequencing technology). The ends of these fragments overlap and, when aligned properly by a genome assembly program, can be used to reconstruct the complete genome. Shotgun sequencing yields sequence data quickly, but the task of assembling the fragments can be quite complicated for larger genomes. For a genome as large as the human genome, it may take many days of CPU time on large-memory, multiprocessor computers to assemble the fragments, and the resulting assembly will usually contain numerous gaps that have to be filled in later. Shotgun sequencing is the method of choice for virtually all genomes sequenced today, and genome assembly algorithms are a critical area of bioinformatics research.

Another aspect of bioinformatics in sequence analysis is annotation, which involves computational gene finding to search for protein-coding genes, RNA genes, and other functional sequences within a genome. Not all of the nucleotides within a genome are genes. Within the genome of higher organisms, large parts of the DNA do not serve any obvious purpose. This so-called junk DNA may, however, contain unrecognized functional elements. Bioinformatics helps to bridge the gap between genome and proteome projects--for example, in the use of DNA sequences for protein identification.

## Genome annotation

In the context of genomics, **annotation** is the process of marking the genes and other biological features in a DNA sequence. The first genome annotation software system was designed in 1995 by Dr. Owen White, who was part of the team at The Institute for Genomic Research that sequenced and analyzed the first genome of a free-living organism to be decoded, the bacterium *Haemophilus influenzae*. Dr. White built a software system to find the genes (places in the DNA sequence that encode a protein), the transfer RNA, and other features, and to make initial assignments of function to those genes. Most current genome annotation systems work similarly, but the programs available for analysis of genomic DNA are constantly changing and improving.

## Computational evolutionary biology

Evolutionary biology is the study of the origin and descent of species, as well as their change over time. Informatics has assisted evolutionary biologists in several key ways; it has enabled researchers to:

- trace the evolution of a large number of organisms by measuring changes in their DNA, rather than through physical taxonomy or physiological observations alone,
- more recently, compare entire genomes, which permits the study of more complex evolutionary events, such as gene duplication, horizontal gene transfer, and the prediction of factors important in bacterial speciation,
- build complex computational models of populations to predict the outcome of the system over time
- track and share information on an increasingly large number of species and organisms

Future work endeavours to reconstruct the now more complex tree of life.

The area of research within computer science that uses genetic algorithms is sometimes confused with computational evolutionary biology, but the two areas are unrelated.

## Analysis of gene expression

The expression of many genes can be determined by measuring mRNA levels with multiple techniques including microarrays, expressed cDNA sequence tag (EST) sequencing, serial analysis of gene expression (SAGE) tag sequencing, massively parallel signature sequencing (MPSS), or various applications of multiplexed in-situ hybridization. All of these techniques are extremely noise-prone and/or subject to bias in the biological measurement, and a major research area in computational biology involves developing statistical tools to separate signal from noise in high-throughput gene expression studies. Such studies are often used to determine the genes implicated in a disorder: one might compare microarray data from cancerous epithelial cells to data from non-cancerous cells to determine the transcripts that are up-regulated and down-regulated in a particular population of cancer cells.

## Analysis of regulation

Regulation is the complex orchestration of events starting with an extracellular signal such as a hormone and leading to an increase or decrease in the activity of one or more proteins. Bioinformatics techniques have been applied to explore various steps in this process. For example, promoter analysis involves the identification and study of sequence motifs in the DNA surrounding the coding region of a gene. These motifs influence the extent to which that region is transcribed into mRNA. Expression data can be used to infer gene regulation: one might compare microarray data from a wide variety of states of an organism to form hypotheses about the genes involved in each state. In a single-cell organism, one might compare stages of the cell cycle, along with various stress conditions (heat shock, starvation, etc.). One can then apply clustering algorithms to that expression data to determine which genes are co-expressed. For example, the upstream regions (promoters) of co-expressed genes can be searched for over-represented regulatory elements.

## Analysis of protein expression

Protein microarrays and high throughput (HT) mass spectrometry (MS) can provide a snapshot of the proteins present in a biological sample. Bioinformatics is very much involved in making sense of protein microarray and HT MS data; the former approach faces similar problems as with microarrays targeted at mRNA, the latter involves the problem of matching large amounts of mass data against predicted masses from protein sequence databases, and the complicated statistical analysis of samples where multiple, but incomplete peptides from each protein are detected.

## Analysis of mutations in cancer

In cancer, the genomes of affected cells are rearranged in complex or even unpredictable ways. Massive sequencing efforts are used to identify previously unknown point mutations in a variety of genes in cancer. Bioinformaticians continue to produce specialized automated systems to manage the sheer volume of sequence data produced, and they create new algorithms and software to compare the sequencing results to the growing collection of human genome sequences and germline polymorphisms. New physical detection technology are employed, such as oligonucleotide microarrays to identify chromosomal gains and losses (called comparative genomic hybridization), and single nucleotide polymorphism arrays to detect known *point mutations*. These detection methods simultaneously measure several hundred thousand sites throughout the genome, and when used in high-throughput to measure thousands of samples, generate terabytes of data per experiment. Again the massive amounts and new types of data generate new opportunities for bioinformaticians. The data is often found to contain considerable variability, or noise, and thus Hidden Markov model and change-point analysis methods are being developed to infer real copy number changes.

Another type of data that requires novel informatics development is the analysis of lesions found to be recurrent among many tumors .

## Prediction of protein structure

Protein structure prediction is another important application of bioinformatics. The amino acid sequence of a protein, the so-called primary structure, can be easily determined from the sequence on the gene that codes for it. In the vast majority of cases, this primary structure uniquely determines a structure in its native environment. (Of course, there are exceptions, such as the bovine spongiform encephalopathy - aka Mad Cow Disease - prion.) Knowledge of this structure is vital in understanding the function of the protein. For lack of better terms, structural information is usually classified as one of *secondary*, *tertiary* and *quaternary* structure. A viable general solution to such predictions remains an open problem. As of now, most efforts have been directed towards heuristics that work most of the time.

One of the key ideas in bioinformatics is the notion of homology. In the genomic branch of bioinformatics, homology is used to predict the function of a gene: if the sequence of gene *A*, whose function is known, is homologous to the sequence of gene *B*, whose function is unknown, one could infer that *B* may share *A*'s function. In the structural branch of bioinformatics, homology is used to determine which parts of a protein are important in structure formation and interaction with other proteins. In a technique called homology modeling, this information is used to predict the structure of a protein once the structure of a homologous protein is known. This currently remains the only way to predict protein structures reliably.

One example of this is the similar protein homology between hemoglobin in humans and the hemoglobin in legumes (leghemoglobin). Both serve the same purpose of transporting oxygen in the organism. Though both of these proteins have completely different amino acid sequences, their protein structures are virtually identical, which reflects their near identical purposes.

Other techniques for predicting protein structure include protein threading and *de novo* (from scratch) physics-based modeling.

*See also:* structural motif and structural domain.

## Comparative genomics

The core of comparative genome analysis is the establishment of the correspondence between genes (orthology analysis) or other genomic features in different organisms. It is these intergenomic maps that make it possible to trace the evolutionary processes responsible for the divergence of two genomes. A multitude of evolutionary events acting at various organizational levels shape genome evolution. At the lowest level, point mutations affect individual nucleotides. At a higher level, large chromosomal segments undergo duplication, lateral transfer, inversion, transposition, deletion and insertion. Ultimately, whole genomes are involved in processes of hybridization, polyploidization and endosymbiosis, often leading to rapid speciation. The complexity of genome evolution poses many exciting challenges to developers of mathematical models and algorithms, who have recourse to a spectra of algorithmic, statistical and mathematical techniques, ranging from exact, heuristics, fixed parameter and approximation algorithms for problems based on parsimony models to Markov Chain Monte Carlo algorithms for Bayesian analysis of problems based on probabilistic models.

Many of these studies are based on the homology detection and protein families computation.

## Modeling biological systems

Systems biology involves the use of computer simulations of cellular subsystems (such as the networks of metabolites and enzymes which comprise metabolism, signal transduction pathways and gene regulatory networks) to both analyze and visualize the complex connections of these cellular processes. Artificial life or virtual evolution attempts to understand evolutionary processes via the computer simulation of simple (artificial) life forms.

## High-throughput image analysis

Computational technologies are used to accelerate or fully automate the processing, quantification and analysis of large amounts of high-information-content biomedical imagery. Modern image analysis systems augment an observer's ability to make measurements from a large or complex set of images, by improving accuracy, objectivity, or speed. A fully developed analysis system may completely replace the observer. Although these systems are not unique to biomedical imagery, biomedical imaging is becoming more important for both diagnostics and research. Some examples are:

- high-throughput and high-fidelity quantification and sub-cellular localization (high-content screening, cytohistopathology)
- morphometrics
- clinical image analysis and visualization
- determining the real-time air-flow patterns in breathing lungs of living animals
- quantifying occlusion size in real-time imagery from the development of and recovery during arterial injury
- making behavioral observations from extended video recordings of laboratory animals
- infrared measurements for metabolic activity determination
- inferring clone overlaps in DNA mapping, e.g. the Sulston score

## Protein-protein docking

In the last two decades, tens of thousands of protein three-dimensional structures have been determined by X-ray crystallography and Protein nuclear magnetic resonance spectroscopy (protein NMR). One central question for the biological scientist is whether it is practical to predict possible protein-protein interactions only based on these 3D shapes, without doing protein-protein interaction experiments. A variety of methods have been developed to tackle the Protein-protein docking problem, though it seems that there is still much work to be done in this field.

## Software and tools

Software tools for bioinformatics range from simple command-line tools, to more complex graphical programs and standalone web-services available from various bioinformatics companies or public institutions.

## Web services in bioinformatics

SOAP and REST-based interfaces have been developed for a wide variety of bioinformatics applications allowing an application running on one computer in one part of the world to use algorithms, data and computing resources on servers in other parts of the world. The main advantages derive from the fact that end users do not have to deal with software and database maintenance overheads.

Basic bioinformatics services are classified by the EBI into three categories: SSS (Sequence Search Services), MSA (Multiple Sequence Alignment) and BSA (Biological Sequence Analysis). The availability of these service-oriented bioinformatics resources demonstrate the applicability of web based bioinformatics solutions, and range from a collection of standalone tools with a common data format under a single, standalone or web-based interface, to integrative, distributed and extensible bioinformatics workflow management systems.

## See also

### Related topics

- Biocybernetics
  - Bioinformatics companies
  - Biologically inspired computing
  - Biomedical informatics
  - Computational biology
  - Computational biomodeling
  - Computational genomics
  - DNA sequencing theory
  - Dot plot (bioinformatics)
  - Dry lab
  - Functional genomics
  - Margaret Oakley Dayhoff
  - Metabolic network modelling
  - Molecular design software
  - Molecular modeling on GPU
  - Morphometrics
  - Natural computation
  - Pharmaceutical company
  - Protein-protein interaction prediction
  - Shredding (disassembling genomic data)
  - List of nucleic acid simulation software
  - List of numerical analysis software
  - List of protein structure prediction software
  - List of scientific journals in bioinformatics
-



## Related fields

- Applied mathematics
- Artificial intelligence
- Biodiversity informatics
- Biology
- Cheminformatics
- Clinomics
- Comparative genomics
- Computational biology
- Computational epigenetics
- Computational science
- Computer science
- Cybernetics
- Ecoinformatics
- Functional genomics
- Genomics
- Informatics (academic field)
- Information theory
- Mathematical biology
- Molecular modelling
- Neuroinformatics
- Proteomics
- Pervasive adaptation
- Scientific computing
- Statistics
- Structural biology
- Systems biology
- Theoretical biology
- Veterinary informatics

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## External links

- Major Organizations
  - Bioinformatics Organization (Bioinformatics.Org): The Open-Access Institute (<http://bioinformatics.org/>)
  - EMBnet (<http://www.embnet.org/>)
  - European Bioinformatics Institute (<http://www.ebi.ac.uk/>)
  - European Molecular Biology Laboratory (<http://www.embl.org/>)
  - The International Society for Computational Biology (<http://www.iscb.org/>)
  - National Center for Biotechnology Information (<http://www.ncbi.nlm.nih.gov/>)
  - Open Bioinformatics Foundation: umbrella non-profit organization supporting certain open-source projects in bioinformatics (<http://www.open-bio.org/>)
  - Swiss Institute of Bioinformatics
  - Wellcome Trust Sanger Institute

- Major Journals
  - Algorithms in Molecular Biology (<http://www.almob.org/>)
  - Bioinformatics (<http://bioinformatics.oupjournals.org/>)
  - BMC Bioinformatics (<http://www.biomedcentral.com/bmcbioinformatics>)
  - Briefings in Bioinformatics (<http://bib.oxfordjournals.org/>)
  - Journal of Advanced Research in Bioinformatics (<http://www.i-asr.org/jarb.html>)
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  - The International Journal of Biostatistics (<http://www.bepress.com/ijb/>)
  - Journal of Computational Biology ([http://www.liebertpub.com/publication.aspx?pub\\_id=31](http://www.liebertpub.com/publication.aspx?pub_id=31))
  - Cancer Informatics ([http://la-press.com/journal.php?pa=description&journal\\_id=10](http://la-press.com/journal.php?pa=description&journal_id=10))
  - Molecular Systems Biology (<http://www.nature.com/msb/index.html>)
  - PLoS Computational Biology (<http://compbiol.plosjournals.org>)
  - Statistical Applications in Genetic and Molecular Biology (<http://www.bepress.com/sagmb/>)
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  - International Journal of Bioinformatics Research and Applications (<http://www.inderscience.com/browse/index.php?journalcode=ijbra>)
  - International Journal of Computational Biology and Drug Design (IJCBD)
  - International Journal of Functional Informatics and Personalized Medicine (IJFIPM)
- Graduate diploma
  - Canada, Montréal : UQAM, Montréal (<http://www.bioinfo.uqam.ca>)
- Other sites
  - The exhaustive bioinformatics information resource directory including servers, tools, database links and bioinformatics companies (<http://bionet.awardspace.info/>)
  - The Collection of Biostatistics Research Archive (<http://www.biostatsresearch.com/repository/>)
  - Human Genome Project and Bioinformatics ([http://www.ornl.gov/TechResources/Human\\_Genome/research/informatics.html](http://www.ornl.gov/TechResources/Human_Genome/research/informatics.html))
  - List of Bioinformatics Research Groups (<http://www.bioinformatics.fr/laboratories.php>) at Bioinformatics.fr
  - List of Bioinformatics Research Groups ([http://www.dmoz.org/Science/Biology/Bioinformatics/Research\\_Groups/](http://www.dmoz.org/Science/Biology/Bioinformatics/Research_Groups/)) at the Open Directory Project
- Tutorials / Resources / Primers
  - Bioinformatics - A Science Primer (<http://www.ncbi.nlm.nih.gov/About/primer/bioinformatics.html>) — by NCBI
  - A bioinformatics directory (<http://bioinformatics.co.nr/>)
  - Canadian Bioinformatics Workshop and Links Directory (<http://bioinformatics.ca/>)

## See also

- International Society of Intelligent Biological Medicine (ISIBM)

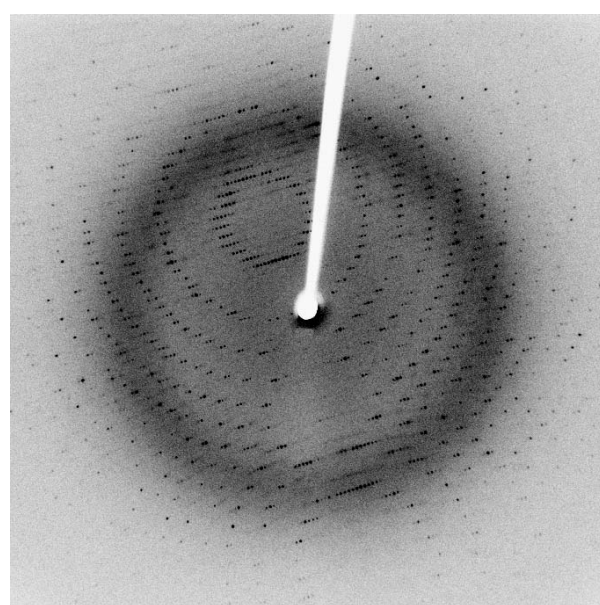
# X-ray diffraction

**X-ray scattering techniques** are a family of non-destructive analytical techniques which reveal information about the crystallographic structure, chemical composition, and physical properties of materials and thin films. These techniques are based on observing the scattered intensity of an X-ray beam hitting a sample as a function of incident and scattered angle, polarization, and wavelength or energy.

## X-ray diffraction techniques

X-ray diffraction finds the geometry or shape of a molecule using X-rays. X-ray diffraction techniques are based on the elastic scattering of X-rays from structures that have long range order. The most comprehensive description of scattering from crystals is given by the dynamical theory of diffraction.<sup>[1]</sup>

- Single-crystal X-ray diffraction is a technique used to solve the complete structure of crystalline materials, ranging from simple inorganic solids to complex macromolecules, such as proteins.
- Powder diffraction (XRD) is a technique used to characterise the crystallographic structure, crystallite size (grain size), and preferred orientation in polycrystalline or powdered solid samples. Powder diffraction is commonly used to identify unknown substances, by comparing diffraction data against a database maintained by the International Centre for Diffraction Data. It may also be used to characterize heterogeneous solid mixtures to determine relative abundance of crystalline compounds and, when coupled with lattice refinement techniques, such as Rietveld refinement, can provide structural information on unknown materials. Powder diffraction is also a common method for determining strains in crystalline materials. An effect of the finite crystallite sizes is seen as a broadening of the peaks in an X-ray diffraction as is explained by the Scherrer Equation.
- Thin film diffraction and grazing incidence X-ray diffraction may be used to characterize the crystallographic structure and preferred orientation of substrate-anchored thin films.
- High-resolution X-ray diffraction is used to characterize thickness, crystallographic structure, and strain in thin epitaxial films. It employs parallel-beam optics.
- X-ray pole figure analysis enables one to analyze and determine the distribution of crystalline orientations within a crystalline thin-film sample.
- X-ray rocking curve analysis is used to quantify grain size and mosaic spread in crystalline materials.



This is an X-ray diffraction pattern formed when X-rays are focused on a crystalline material, in this case a protein. Each dot, called a reflection, forms from the coherent interference of scattered X-rays passing through the crystal.

## Scattering techniques

### Elastic scattering

Materials that do not have long range order may also be studied by scattering methods that rely on elastic scattering of monochromatic X-rays.

- Small angle X-ray scattering (SAXS) probes structure in the nanometer to micrometer range by measuring scattering intensity at scattering angles  $2\theta$  close to  $0^\circ$ .<sup>[2]</sup>
- X-ray reflectivity is an analytical technique for determining thickness, roughness, and density of single layer and multilayer thin films.
- Wide angle X-ray scattering (WAXS), a technique concentrating on scattering angles  $2\theta$  larger than  $5^\circ$ .

### Inelastic scattering

When the energy and angle of the inelastically scattered X-rays are monitored scattering techniques can be used to probe the electronic band structure of materials.

- Compton scattering
- Resonant inelastic X-ray scattering (RIXS)
- X-ray Raman scattering
- X-ray diffraction pattern

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### See also

- Structure determination
- Materials Science
- Metallurgy
- Mineralogy
- X-ray crystallography
- X-ray generator

### External links

- International Union of Crystallography<sup>[3]</sup>
  - IUCr Crystallography Online<sup>[4]</sup>
- The International Centre for Diffraction Data (ICDD)<sup>[5]</sup>
- Archives of XRD@JISCMail.AC.UK<sup>[6]</sup>
- The British Crystallographic Association<sup>[7]</sup>
- Introduction to X-ray Diffraction<sup>[8]</sup> at University of California, Santa Barbara

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- [2] Glatter, O.; O. Kratky (1982). *Small Angle X-ray Scattering* (<http://physchem.kfunigraz.ac.at/sm/Software.htm>). Academic Press. .
- [3] <http://www.iucr.ac.uk/>
- [4] <http://www.iucr.org/cww-top/crystal.index.html>
- [5] <http://www.icdd.com/>
- [6] <http://www.jiscmail.ac.uk/lists/xrd.html>
- [7] <http://crystallography.org.uk/>
- [8] <http://www.mrl.ucsb.edu/mrl/centralfacilities/xray/xray-basics/index.html>

## 2D-FT NMRI and spectroscopy

**2D-FT Nuclear magnetic resonance imaging (2D-FT NMRI)**, or **two-dimensional Fourier transform** nuclear magnetic resonance imaging (**NMRI**), is primarily a non-invasive imaging technique most commonly used in biomedical research and medical radiology to visualize structures and functions of the living systems and single cells. The physical principle<sup>[1]</sup> is essentially the same in N(MRI), nuclear magnetic resonance, FT (NMR) spectroscopy, topical NMR, or even in electron spin resonance (ESR); however, the details are significantly different at present for ESR, as only in the early days of NMR the static magnetic field was scanned for obtaining spectra, as it is still the case in many ESR spectrometers. NMRI, on the other hand, often utilizes a linear magnetic field gradient to obtain an image that combines the visualization of molecular structure and dynamics. It is this dynamic aspect of NMRI, as well as its highest sensitivity for the  $^1\text{H}$  nucleus that distinguishes it very dramatically from X-ray CAT scanning that 'misses' hydrogens because of their very low X-ray scattering factor.

### Chemical Shifts

NMR is a very useful family of techniques for chemical and biochemical research because of the chemical shift; this effect consists in a frequency shift of the nuclear magnetic resonance for specific chemical groups or atoms as a result of the partial shielding of the corresponding nuclei from the applied, static external magnetic field by the electron orbitals (or molecular orbitals) surrounding such nuclei present in the chemical groups. Thus, the higher the electron density surrounding a specific nucleus the larger the chemical shift will be.

The resulting magnetic field at the

nucleus is thus lower than the applied external magnetic field and the resonance frequencies observed as a result of such shielding are lower than the value that would be observed in the absence of any electronic orbital shielding. Furthermore, in order to obtain a chemical shift value independent of the strength of the applied magnetic field and allow for the direct comparison of spectra obtained at different magnetic field values, the chemical shift is defined by the ratio of the strength of the local magnetic field value at the observed (electron orbital-shielded) nucleus by the



Advanced 3 T clinical diagnostics and biomedical research NMR Imaging instrument.

external magnetic field strength,  $\mathbf{H}_{\text{loc}} / \mathbf{H}_0$ . The first NMR observations of the chemical shift, with the correct physical chemistry interpretation, were reported for  $^{19}\text{F}$  containing compounds in the early 1950s by Herbert S. Gutowsky and Charles P. Slichter from the University of Illinois at Urbana (USA).

A related effect in metals is called the Knight shift, which is due only to the conduction electrons. Such conduction electrons present in metals induce an "additional" local field at the nuclear site, due to the spin re-orientation of the conduction electrons in the presence of the applied (constant), external magnetic field. This is only broadly 'similar' to the chemical shift in either solutions or diamagnetic solids.

## Two-dimensional Fourier transform imaging and spectroscopy

2D-FT analysis is a very powerful method for both NMRI and two-dimensional nuclear magnetic resonance spectroscopy (2D-FT NMRS)<sup>[2]</sup> that allows the three-dimensional reconstruction of polymer and biopolymer structures at atomic resolution<sup>[3]</sup> for molecular weights (Mw) of dissolved biopolymers in aqueous solutions (for example) up to about 50,000 MW. For larger biopolymers or polymers, more complex methods have been developed to obtain limited structural resolution needed for partial 3D-reconstructions of higher molecular structures, e.g. for up to 900,000 MW or even oriented microcrystals in aqueous suspensions or single crystals; such methods have also been reported for *in vivo* 2D-FT NMR spectroscopic studies of algae, bacteria, yeast and certain mammalian cells, including human ones.

### 2D-FT Definition

A 2D-FT, or two-dimensional Fourier transform, transforms a function of two temporal variables into a function of two frequency variables. In MRS the frequencies relate to the resonant frequency offsets caused by chemical shift or J-coupling. In MRI a resonance frequency offset is introduced as a function of position; the frequency variables in the Fourier transformed time-data correspond to spatial location in the final image.<sup>[4]</sup>

### Example

A 2D Fourier transformation and phase correction is applied to a set of 2D NMR (FID) signals:  $s(t_1, t_2)$  yielding a real 2D-FT NMR 'spectrum' (collection of 1D FT-NMR spectra) represented by a matrix  $\mathbf{S}$  whose elements are

$$S(\nu_1, \nu_2) = \text{Re} \int \int \cos(\nu_1 t_1) \exp(-i\nu_2 t_2) s(t_1, t_2) dt_1 dt_2$$

where  $\nu_1$  and  $\nu_2$  denote the discrete indirect double-quantum and single-quantum(detection) axes, respectively, in the 2D NMR experiments. Next, the *covariance matrix* is calculated in the frequency domain according to the following equation

$$\mathbf{C}(\nu'_2, \nu_2) = \mathbf{S}^T \mathbf{S} = \sum_{\nu_1} [S(\nu_1, \nu'_2) S(\nu_1, \nu_2)],$$

with  $\nu_2, \nu'_2$  taking all possible single-quantum frequency values and with the summation carried out over all discrete, double quantum frequencies  $\nu_1$ .

## Brief explanation of NMRI diagnostic uses in Pathology

As an example, a diseased tissue such as a malignant tumor, can be detected by 2D-FT NMRI because the hydrogen nuclei of molecules in different tissues return to their equilibrium spin state at different relaxation rates, and also because of the manner in which a malignant tumor spreads and grows rapidly along the blood vessels adjacent to the tumor, also inducing further vascularization to occur. By changing the pulse delays in the RF pulse sequence employed, and/or the RF pulse sequence itself, one may obtain a 'relaxation—based contrast', or contrast enhancement between different types of body tissue, such as normal vs. diseased tissue cells for example.

## See also

- Nuclear magnetic resonance (NMR)
- Edward Mills Purcell
- Felix Bloch
- Medical imaging
- Paul C. Lauterbur
- Magnetic resonance microscopy
- Peter Mansfield
- Computed tomography (CT)
- Solid-state NMR
- Knight shift
- John Hasbrouck Van Vleck
- Chemical shift
- Herbert S. Gutowsky
- John S. Waugh
- Charles Pence Slichter
- Protein nuclear magnetic resonance spectroscopy
- Kurt Wüthrich
- Nuclear Overhauser effect
- Fourier transform spectroscopy(FTS)
- Jean Jeneer
- Richard R. Ernst
- FT-NIRS (NIR)
- Magnetic resonance elastography
- Relaxation
- Earth's field NMR (EFNMR)
- Robinson oscillator

## Further Reading

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- Charles P. Slichter.1996. *Principles of Magnetic Resonance.* Springer: Berlin and New York, Third Edition., 651pp. ISBN 0-387-50157-6.
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- Protein structure determination in solution by NMR spectroscopy <sup>[6]</sup> Kurt Wüthrich. J Biol Chem. 1990 December 25;265(36):22059-62
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- Peter Mansfield. 2003.Nobel Laureate in Physiology and Medicine for (2D and 3D) MRI <sup>[8]</sup>
- D. Benett. 2007. PhD Thesis. Worcester Polytechnic Institute. PDF of 2D-FT Imaging Applications to NMRI in Medical Research. <sup>[9]</sup> Worcester Polytechnic Institute. (Includes many 2D-FT NMR images of human brains.)
- Paul Lauterbur. 2003.Nobel Laureate in Physiology and Medicine for (2D and 3D) MRI. <sup>[10]</sup>
- Jean Jeener. 1971. Two-dimensional Fourier Transform NMR, presented at an Ampere International Summer School, Basko Polje, unpublished. A verbatim quote follows from Richard R. Ernst's Nobel Laureate Lecture delivered on December 2, 1992, "A new approach to measure two-dimensional (2D) spectra." has been proposed by Jean Jeener at an Ampere Summer School in Basko Polje, Yugoslavia, 1971 (Jean Jeneer,1971)). He suggested a 2D Fourier transform experiment consisting of two  $\pi/2$  pulses with a variable time  $t_1$  between the pulses and the time variable  $t_2$  measuring the time elapsed after the second pulse as shown in Fig. 6 that expands the principles of Fig. 1. Measuring the response  $S(t_1, t_2)$  of the two-pulse sequence and Fourier-transformation with respect to both time variables produces a two-dimensional spectrum  $S(O_1, O_2)$  of the desired form. This two-pulse experiment by Jean Jeener is the forefather of a whole class of 2D experiments that can also easily be expanded to multidimensional spectroscopy.



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## External links

- Cardiac Infarct or "heart attack" Imaged in Real Time by 2D-FT NMRI<sup>[18]</sup>
- Interactive Flash Animation on MRI<sup>[19]</sup> - *Online Magnetic Resonance Imaging physics and technique course*
- Herbert S. Gutowsky
- Jiri Jonas and Charles P. Slichter: NMR Memoires at [[NAS<sup>[20]</sup>] about Herbert Sander Gutowsky; NAS = National Academy of Sciences, USA, ]
- 3D Animation Movie about MRI Exam<sup>[21]</sup>
- International Society for Magnetic Resonance in Medicine<sup>[22]</sup>
- Danger of objects flying into the scanner<sup>[23]</sup>

## Related Wikipedia websites

- Medical imaging
- Computed tomography
- Magnetic resonance microscopy
- Fourier transform spectroscopy
- FT-NIRS
- Chemical imaging
- Magnetic resonance elastography
- Nuclear magnetic resonance (NMR)
- Chemical shift
- Relaxation
- Robinson oscillator
- Earth's field NMR (EFNMR)
- Rabi cycle

*This article incorporates material by the original author from 2D-FT MR- Imaging and related Nobel awards<sup>[24]</sup> on PlanetPhysics<sup>[25]</sup>, which is licensed under the GFDL.*

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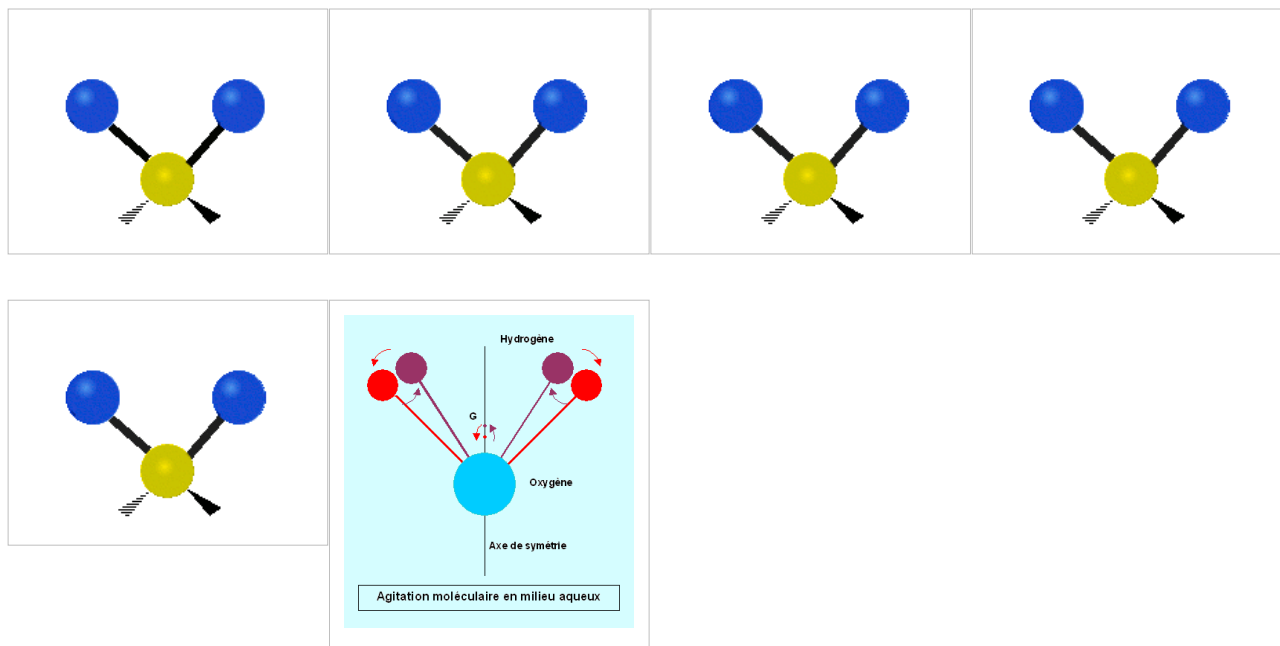
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- [9] <http://www.wpi.edu/Pubs/ETD/Available/etd-081707-080430/unrestricted/dbennett.pdf>
- [10] [http://nobelprize.org/nobel\\_prizes/medicine/laureates/2003/lauterbur-lecture.html](http://nobelprize.org/nobel_prizes/medicine/laureates/2003/lauterbur-lecture.html)
- [11] <http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=1568902>
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- [17] <http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=15521>
- [18] [http://www.mr-tip.com/exam\\_gifs/cardiac\\_infarct\\_short\\_axis\\_cine\\_6.gif](http://www.mr-tip.com/exam_gifs/cardiac_infarct_short_axis_cine_6.gif)
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- [20] <http://books.nap.edu/html/biomems/hgutowsky.pdf>
- [21] <http://www.patencys.com/MRI/>
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- [23] [http://www.simplyphysics.com/flying\\_objects.html](http://www.simplyphysics.com/flying_objects.html)
- [24] <http://planetphysics.org/encyclopedia/2DFTImaging.html>
- [25] <http://planetphysics.org/>

# Vibrational circular dichroism

**Vibrational circular dichroism** (VCD) is a spectroscopic technique which detects differences in attenuation of left and right circularly polarized light passing through a sample. It is basically circular dichroism spectroscopy in the infrared and near infrared ranges<sup>[1]</sup>.

Because VCD is sensitive to the mutual orientation of distinct groups in a molecule, it provides three-dimensional structural information. Thus, it is a powerful technique as VCD spectra of enantiomers can be simulated using *ab initio* calculations, thereby allowing the identification of absolute configurations of small molecules in solution from VCD spectra. Among such quantum computations of VCD spectra resulting from the chiral properties of small organic molecules are those based on density functional theory (DFT) and gauge-invariant atomic orbitals (GIAO). As a simple example of the experimental results that were obtained by VCD are the spectral data obtained within the carbon-hydrogen (C-H) stretching region of 21 amino acids in heavy water solutions. Measurements of vibrational optical activity (VOA) have thus numerous applications, not only for small molecules, but also for large and complex biopolymers such as muscle proteins (myosin, for example) and DNA.

## Vibrational modes



## Theory of VCD

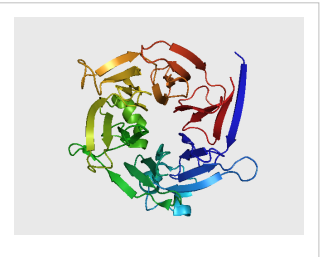
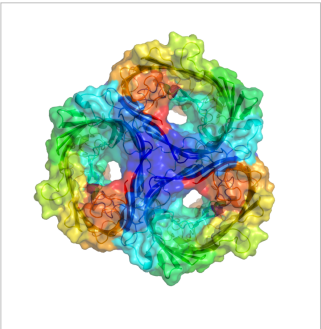
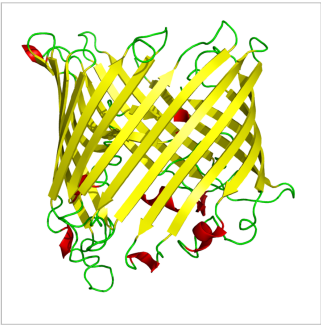
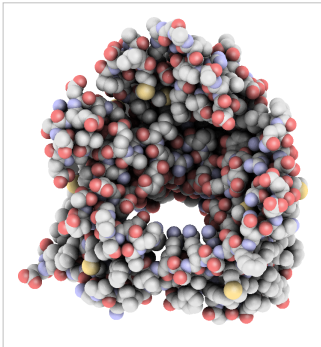
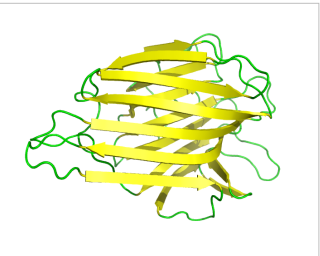
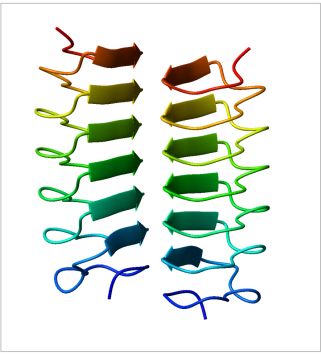
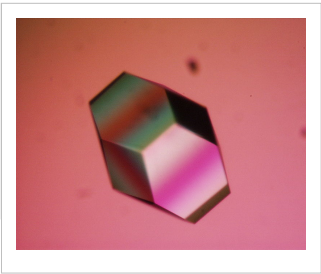
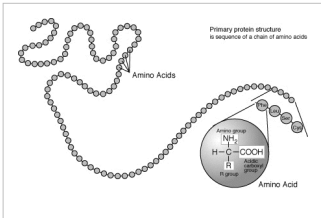
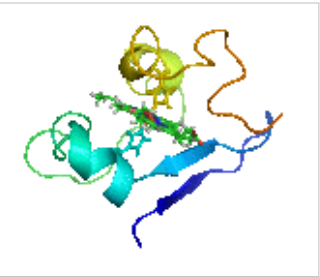
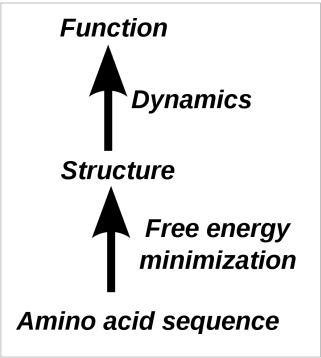
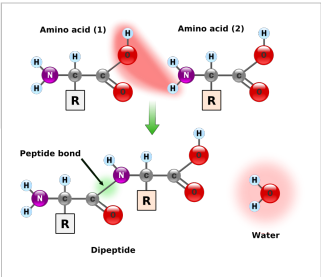
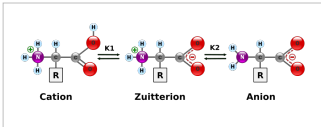
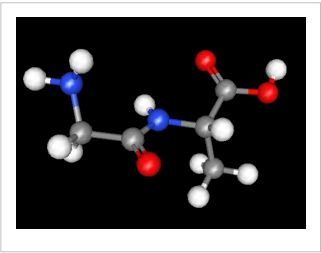
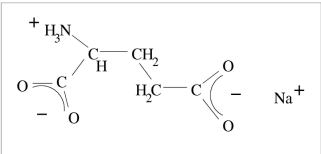
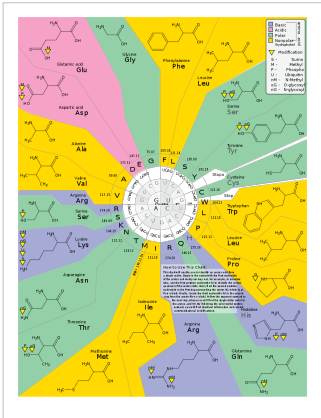
While the fundamental quantity associated with the infrared absorption is the dipole strength, the differential absorption is proportional also to the rotational strength, a quantity which depends on both the electric and magnetic dipole transition moments. Sensitivity of the handedness of a molecule toward circularly polarized light results from the form of the rotational strength.

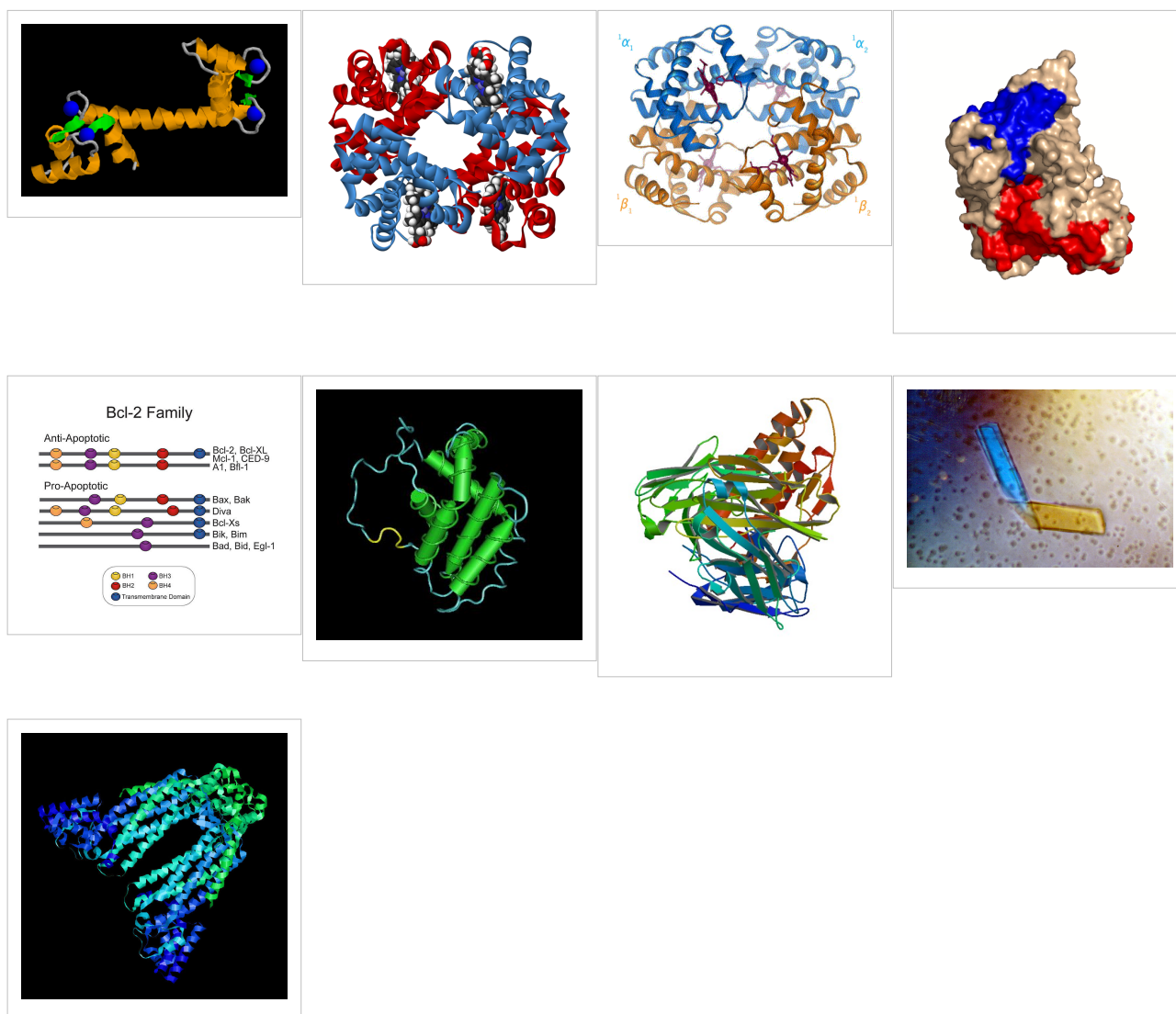
## VCD of peptides and proteins

Extensive VCD studies have been reported for both polypeptides and several proteins in solution<sup>[2] [3] [4]</sup>; several recent reviews were also compiled<sup>[5] [6] [7] [8]</sup>. An extensive but not comprehensive VCD publications list is also provided in the "References" section. The published reports over the last 22 years have established VCD as a powerful technique with improved results over those previously obtained by visible/UV circular dichroism (CD) or

optical rotatory dispersion (ORD) for proteins and nucleic acids.

Amino acid and polypeptide structures





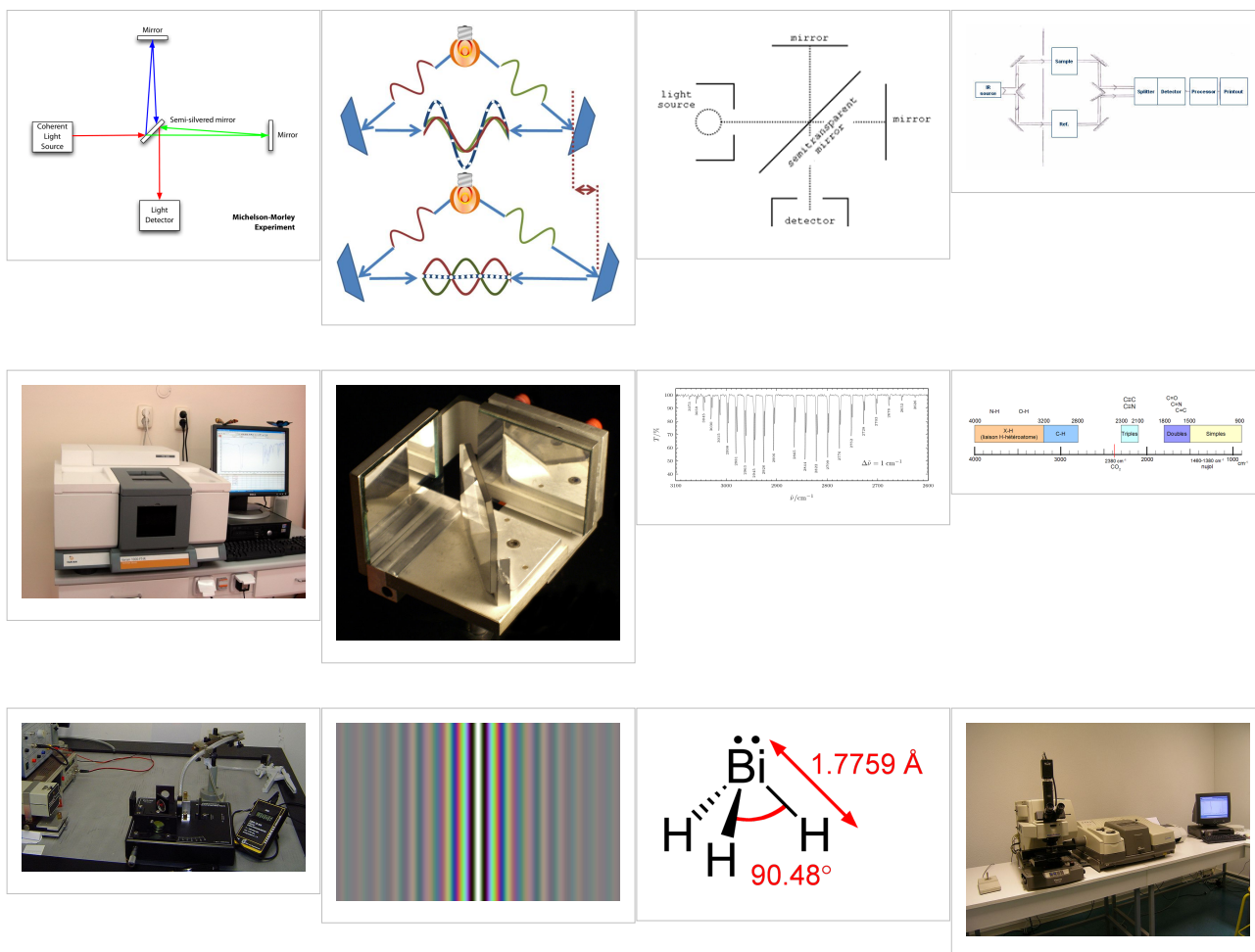
## VCD of nucleic acids

VCD spectra of nucleotides, synthetic polynucleotides and several nucleic acids, including DNA, have been reported and assigned in terms of the type and number of helices present in A-, B-, and Z- DNA.

## VCD Instrumentation

For biopolymers such as proteins and nucleic acids, the difference in absorbance between the levo- and dextro-configurations is five orders of magnitude smaller than the corresponding (unpolarized) absorbance. Therefore, VCD of biopolymers requires the use of very sensitive, specially built instrumentation as well as time-averaging over relatively long intervals of time even with such sensitive VCD spectrometers. Most CD instruments produce left- and right- circularly polarized light which is then either sine-wave or square-wave modulated, with subsequent phase-sensitive detection and lock-in amplification of the detected signal. In the case of FT-VCD, a photo-elastic modulator (PEM) is employed in conjunction with an FT-IR interferometer set-up. An example is that of a Bomem model MB-100 FT-IR interferometer equipped with additional polarizing optics/ accessories needed for recording VCD spectra. A parallel beam emerges through a side port of the interferometer which passes first through a wire grid linear polarizer and then through an octagonal-shaped ZnSe crystal PEM which modulates the polarized beam at a fixed, lower frequency such as 37.5 kHz. A mechanically stressed crystal such as ZnSe exhibits birefringence when stressed by an adjacent piezoelectric transducer. The linear polarizer is positioned close to, and at 45 degrees, with

respect to the ZnSe crystal axis. The polarized radiation focused onto the detector is doubly modulated, both by the PEM and by the interferometer setup. A very low noise detector, such as MCT (HgCdTe), is also selected for the VCD signal phase-sensitive detection. Quasi-complete commercial FT-VCD instruments are also available from a few manufacturers but these are quite expensive and also have to be still considered as being at the prototype stage. To prevent detector saturation an appropriate, long wave pass filter is placed before the very low noise MCT detector, which allows only radiation below  $1750\text{ cm}^{-1}$  to reach the MCT detector; the latter however measures radiation only down to  $750\text{ cm}^{-1}$ . FT-VCD spectra accumulation of the selected sample solution is then carried out, digitized and stored by an in-line computer. Published reviews that compare various VCD methods are also available.<sup>[9] [10]</sup>



## Magnetic VCD

VCD spectra have also been reported in the presence of an applied external magnetic field<sup>[11]</sup>. This method can enhance the VCD spectral resolution for small molecules<sup>[12] [13] [14] [15] [16]</sup>.

## Raman optical activity (ROA)

ROA is a technique complementary to VCD especially useful in the 50—1600 cm<sup>-1</sup> spectral region; it is considered as the technique of choice for determining optical activity for photon energies less than 600 cm<sup>-1</sup>.

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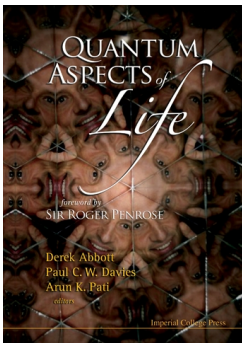
## See also

- Circular dichroism
  - Birefringence
  - Optical rotatory dispersion
  - IR spectroscopy
  - Polarization
  - Proteins
  - Nucleic Acids
  - DNA
  - Molecular models of DNA
  - DNA structure
  - Protein structure
  - Amino acids
  - Density functional theory
  - Quantum chemistry
  - Raman optical activity (ROA)
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# Quantum Aspects of Life

| <i>Quantum Aspects of Life</i>                                                    |                                                                                              |
|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|
|  |                                                                                              |
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*Quantum Aspects of Life* is a science text, with a foreword by Sir Roger Penrose, which notably explores the open question of the role of quantum mechanics at molecular scales of relevance to biology. The book adopts a debate-like style and contains chapters written by various world-experts; giving rise to both a mix of both skeptical and sympathetic viewpoints. The book notably addresses questions of quantum physics, biophysics, nanoscience, quantum chemistry, mathematical biology, complexity theory, and philosophy that are inspired by the 1944 seminal book *What Is Life?* by Erwin Schrödinger.

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## See also

- Quantum biology
- Erwin Schrödinger
- *What Is Life?*

## External links

- Book's homepage at ICP<sup>[5]</sup>

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# Quantum Biochemistry

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**Quantum chemistry** is a branch of theoretical chemistry, which applies quantum mechanics and quantum field theory to address problems in chemistry. The description of the electronic behavior of atoms and molecules as pertaining to their reactivity is one of the applications of quantum chemistry. Quantum chemistry lies on the border between chemistry and physics, and significant contributions have been made by scientists from both fields. It has a strong and active overlap with the field of atomic physics and molecular physics, as well as physical chemistry.

Quantum chemistry mathematically describes the fundamental behavior of matter at the molecular scale.<sup>[1]</sup> It is, in principle, possible to describe all chemical systems using this theory. In practice, only the simplest chemical systems may realistically be investigated in purely quantum mechanical terms, and approximations must be made for most practical purposes (e.g., Hartree-Fock, post Hartree-Fock or Density functional theory, see computational chemistry for more details). Hence a detailed understanding of quantum mechanics is not necessary for most chemistry, as the important implications of the theory (principally the orbital approximation) can be understood and applied in simpler terms.

In quantum mechanics the Hamiltonian, or the physical state, of a particle can be expressed as the sum of two operators, one corresponding to kinetic energy and the other to potential energy. The Hamiltonian in the Schrödinger wave equation used in quantum chemistry does not contain terms for the spin of the electron.

Solutions of the Schrödinger equation for the hydrogen atom gives the form of the wave function for atomic orbitals, and the relative energy of the various orbitals. The orbital approximation can be used to understand the other atoms e.g. helium, lithium and carbon.

## History

The **history of quantum chemistry** essentially began with the 1838 discovery of cathode rays by Michael Faraday, the 1859 statement of the black body radiation problem by Gustav Kirchhoff, the 1877 suggestion by Ludwig Boltzmann that the energy states of a physical system could be discrete, and the 1900 quantum hypothesis by Max Planck that any energy radiating atomic system can theoretically be divided into a number of discrete energy elements  $\epsilon$  such that each of these energy elements is proportional to the frequency  $\nu$  with which they each individually radiate energy, as defined by the following formula:

$$\epsilon = h\nu$$

where  $h$  is a numerical value called Planck's Constant. Then, in 1905, to explain the photoelectric effect (1839), i.e., that shining light on certain materials can function to eject electrons from the material, Albert Einstein postulated, based on Planck's quantum hypothesis, that light itself consists of individual quantum particles, which later came to be called photons (1926). In the years to follow, this theoretical basis slowly began to be applied to chemical structure, reactivity, and bonding.

## Electronic structure

The first step in solving a quantum chemical problem is usually solving the Schrödinger equation (or Dirac equation in relativistic quantum chemistry) with the electronic molecular Hamiltonian. This is called determining the **electronic structure** of the molecule. It can be said that the electronic structure of a molecule or crystal implies essentially its chemical properties. An exact solution for the Schrödinger equation can only be obtained for the hydrogen atom. Since all other atomic, or molecular systems, involve the motions of three or more "particles", their Schrödinger equations cannot be solved exactly and so approximate solutions must be sought.



## Wave model

The foundation of quantum mechanics and quantum chemistry is the **wave model**, in which the atom is a small, dense, positively charged nucleus surrounded by electrons. Unlike the earlier Bohr model of the atom, however, the wave model describes electrons as "clouds" moving in orbitals, and their positions are represented by probability distributions rather than discrete points. The strength of this model lies in its predictive power. Specifically, it predicts the pattern of chemically similar elements found in the periodic table. The wave model is so named because electrons exhibit properties (such as interference) traditionally associated with waves. See wave-particle duality.

## Valence bond

Although the mathematical basis of quantum chemistry had been laid by Schrödinger in 1926, it is generally accepted that the first true calculation in quantum chemistry was that of the German physicists Walter Heitler and Fritz London on the hydrogen ( $H_2$ ) molecule in 1927. Heitler and London's method was extended by the American theoretical physicist John C. Slater and the American theoretical chemist Linus Pauling to become the **Valence-Bond (VB)** [or **Heitler-London-Slater-Pauling (HLSP)**] method. In this method, attention is primarily devoted to the pairwise interactions between atoms, and this method therefore correlates closely with classical chemists' drawings of bonds.

## Molecular orbital

An alternative approach was developed in 1929 by Friedrich Hund and Robert S. Mulliken, in which electrons are described by mathematical functions delocalized over an entire molecule. The **Hund-Mulliken** approach or **molecular orbital (MO) method** is less intuitive to chemists, but has turned out capable of predicting spectroscopic properties better than the VB method. This approach is the conceptional basis of the **Hartree-Fock method** and further post Hartree-Fock methods.

## Density functional theory

The **Thomas-Fermi model** was developed independently by Thomas and Fermi in 1927. This was the first attempt to describe many-electron systems on the basis of electronic density instead of wave functions, although it was not very successful in the treatment of entire molecules. The method did provide the basis for what is now known as **density functional theory**. Though this method is less developed than post Hartree-Fock methods, its lower computational requirements allow it to tackle larger polyatomic molecules and even macromolecules, which has made it the most used method in computational chemistry at present.

## Chemical dynamics

A further step can consist of solving the Schrödinger equation with the total molecular Hamiltonian in order to study the motion of molecules. Direct solution of the Schrödinger equation is called *quantum molecular dynamics*, within the semiclassical approximation *semiclassical molecular dynamics*, and within the classical mechanics framework *molecular dynamics (MD)*. Statistical approaches, using for example Monte Carlo methods, are also possible.

## Adiabatic chemical dynamics

In **adiabatic dynamics**, interatomic interactions are represented by single scalar potentials called potential energy surfaces. This is the Born-Oppenheimer approximation introduced by Born and Oppenheimer in 1927. Pioneering applications of this in chemistry were performed by Rice and Ramsperger in 1927 and Kassel in 1928, and generalized into the RRKM theory in 1952 by Marcus who took the transition state theory developed by Eyring in 1935 into account. These methods enable simple estimates of unimolecular reaction rates from a few characteristics of the potential surface.

## Non-adiabatic chemical dynamics

**Non-adiabatic dynamics** consists of taking the interaction between several coupled potential energy surface (corresponding to different electronic quantum states of the molecule). The coupling terms are called **vibronic couplings**. The pioneering work in this field was done by Stueckelberg, Landau, and Zener in the 1930s, in their work on what is now known as the Landau-Zener transition. Their formula allows the transition probability between two diabatic potential curves in the neighborhood of an avoided crossing to be calculated.

## Quantum chemistry and quantum field theory

The application of quantum field theory (QFT) to chemical systems and theories has become increasingly common in the modern physical sciences. One of the first and most fundamentally explicit appearances of this is seen in the theory of the photomagnetron. In this system, plasmas, which are ubiquitous in both physics and chemistry, are studied in order to determine the basic quantization of the underlying bosonic field. However, quantum field theory is of interest in many fields of chemistry, including: nuclear chemistry, astrochemistry, sonochemistry, and quantum hydrodynamics. Field theoretic methods have also been critical in developing the ab initio Effective Hamiltonian theory of semi-empirical pi-electron methods.

## See also

- Atomic physics
- Computational chemistry
- Condensed matter physics
- International Academy of Quantum Molecular Science
- Molecular modelling
- Physical chemistry
- Quantum chemistry computer programs
- Quantum electrochemistry
- QMC@Home
- Theoretical physics

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## External links

- The Sherrill Group - Notes <sup>[2]</sup>
- ChemViz Curriculum Support Resources <sup>[3]</sup>
- Early ideas in the history of quantum chemistry <sup>[4]</sup>
- The Particle Adventure <sup>[5]</sup>

## Nobel lectures by quantum chemists

- Walter Kohn's Nobel lecture <sup>[6]</sup>
- Rudolph Marcus' Nobel lecture <sup>[7]</sup>
- Robert Mulliken's Nobel lecture <sup>[8]</sup>
- Linus Pauling's Nobel lecture <sup>[9]</sup>
- John Pople's Nobel lecture <sup>[10]</sup>

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# Quantum evolution (alternative)

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**Quantum evolution** is the hypothesis that genetic mutation can be adaptive, or directed through quantum effects.<sup>[1]</sup> It should not be confused with quantum evolution, a theory related to the modern evolutionary synthesis. The first publication on this subject, which appeared in a peer review journal, is by Vasily Ogryzko<sup>[2]</sup>. Biologist Johnjoe McFadden and the physicist Jim Al-Khalili subsequently published their own theory in 1999<sup>[3]</sup> in which they proposed a mechanism based on enhanced decoherence of quantum states that interact strongly with the environment. McFadden published his book "Quantum Evolution" in 2000.<sup>[1]</sup>

## Background

The "classical" Darwinian model of the evolution of cells is based on a mechanism whereby cells individually undergo mutation, with the process of natural selection then culling out those mutations which are less beneficial to the organism. **Quantum evolution** is an attempt to provide a theoretical mechanism which would skew these random mutations in favor of some outcome beneficial to the cell.

It should be stated at the outset that this theory would only be useful if indeed there were evidence that some sort of adaptive mutation occurs - in other words, if there were experimental data showing that the classical model of random mutation is lacking, and that certain mutations are "preferred" (occur more frequently) *because* they confer a greater benefit to the organism. This is in and of itself a controversial subject; as a plethora of papers have been published on the enigmatic phenomenon of adaptive mutation and the issue of their origin and mechanism remains unresolved. To date there is no such generally accepted explanation of the mechanism of adaptive mutation although most experimentalists would favour a process of random mutation accompanied by recombination and/or selection.

The mechanism proposed by quantum evolution is to imagine that the configuration of DNA in a cell is held in a quantum superposition of states, and that "mutations" occur as a result of a collapse of the superposition into the "best" configuration for the cell. The proponents of this approach liken the operation of DNA to the operation of a quantum computer, which selects one from a multitude of possible outcomes.

Several problems need to be overcome for this theory to be consistent with our current knowledge of quantum physics. Most importantly, the state of quantum superposition must last long enough to allow the DNA to do its normal job (produce RNA); otherwise, there would be no way for a comparison of the various outcomes of various mutations to occur, and thus no basis for the system to "decide" which mutations are more useful. Protein formation occurs at a rate of on the order of 10,000 times a second ( $10^{-5}$  seconds per protein formed). However, DNA is not translated directly into protein, instead DNA is transcribed into a messenger RNA and this RNA copy is then used for protein biosynthesis. A gene is therefore never directly linked to its protein product, making any possible mechanism for how a signal could be transmitted from a protein to the DNA that encodes it hard to imagine.

Although some have, by analogy to the technique of NMR imaging, posed state coherence times as long as half a second,<sup>[1]</sup> this analysis has been challenged<sup>[4]</sup> (but see also McFadden and Al-Khalili's rebuttal<sup>[5]</sup>) and coherence times on the order of  $10^{-13}$  seconds seems to be a much more realistic outcome. This latter time would be far too short by many orders of magnitude for the protein formation required for a superposition of quantum states to affect mutations.

However recent evidence indicates that quantum coherence of electrons and protons does indeed occur in some (maybe all) enzyme reactions in living cells, such as those involved in photosynthesis<sup>[6]</sup> and may even be responsible for the huge catalytic enhancement of reaction rates provided by enzymes<sup>[7]</sup>.

If the theory of quantum evolution were indeed true, one could further speculate that a similar, more robust process could explain observed phenomena such as the apparent "jumps" in the fossil record as adaptive mutations on an even larger scale; this would require even longer periods of state coherence than those described by McFadden et al.<sup>[1]</sup> yet this has not been proposed by any of the advocates of quantum evolution who have limited their

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speculations to molecular processes.

A different critique on quantum evolution can be made by asking why, if the cell can make use of quantum superpositions, it's not used for more purposes? Our immune system contains "general" agents that attack anything foreign and "specialised" ones (antibodies) that bind to specific proteins on specific bacteria. The latter must be made on demand. But why not use quantum superpositions to immediately attack the bacteria with every conceivable antibody at the same time and select the one that works? The answer is likely to be that more complex systems (than single protons in DNA or electrons and protons in enzymes) cannot be maintained in quantum coherent states for long enough to have biological significance.

Science fiction writer Greg Egan, in his book *Teranesia*, posited a similar mechanism, whereby large adaptive mutations occur in multiple species under the aggressive quantum mechanical influence of a new protein.

## Controversy

A primer on quantum mechanics (such as from David J. Griffiths' "Introduction to Quantum Mechanics") suggests that the very notion of having a molecule choose a state over all others purely based on what an exterior system, with no simultaneous effects on said molecule, is completely contrary to how quantum mechanics works. Quantum mechanical states are dependent on things like energy and other physical phenomena. Furthermore, imposing a viewpoint that one outcome is best implies that a best configuration needs some formal definition that is independent of mentioning organism lifespan, reproductivity, etc (as quantum mechanics does not depend on those things) and that the best configuration does depend on things such as energy levels, perturbations to the molecule, and similar things. When all of these are taken into consideration then the best state would seem to yield a truly random mutation as per what is perceived by humans as evolution.

However, the theory, at least that proposed by McFadden and Al-Khalili <sup>[8]</sup>, did not propose that certain states are identified as 'best' by the quantum system but only that certain states interact with the environment more strongly than other states and thereby promote more rapid decoherence. For a starving cell, these more interactive states are those DNA states that encode mutations that allow the cell to grow.

Of course, DNA, like all molecules, already obeys the laws of quantum mechanics, including quantum superpositions, collapses, and tunneling. The consequences of these laws are more commonly known as quantum chemistry, which explains all of the familiar chemical laws. Since the chemical behavior of DNA is reasonably well-understood, and already includes both (ordinary) quantum mechanics and (ordinary) mutations, it is not yet clear where the additional effects of quantum evolution are supposed to arise.

## See also

- Quantum mechanics
- Quantum mind
- Adaptive mutation

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## Quantum evolution

*For the alternative non-standard theory see: Quantum evolution (alternative).*

**Quantum evolution** is a component of George Gaylord Simpson's multi-tempoed theory of evolutionary change, responsible for the rapid emergence of higher taxonomic groups. According to Simpson, evolutionary rates differ from group to group and even among closely related lineages. These different rates of evolutionary change were designated by Simpson as *horotelic* (medium tempo), *bradytelic* (slow tempo), and *tachytelic* (rapid tempo). Quantum evolution differed from these styles of change in that it involved a drastic shift in the adaptive zones of certain classes of animals. The word "quantum" therefore refers to an "all-or-none reaction," where transitional forms are particularly unstable, and perished rapidly and completely. Although quantum evolution may happen at any taxonomic level (1953, 389), it plays a much larger role in "the origin taxonomic units of relatively high rank, such as families, orders, and classes." (1944, 206)

According to Simpson (1944) quantum evolution relied heavily upon Sewall Wright's theory of random genetic drift. Simpson believed that major evolutionary transitions would arise when small populations—isolated and limited from gene flow—would fixate upon unusual gene combinations. This "inadaptive phase" (by genetic drift) would then (by natural selection) drive a deme population from one stable adaptive peak to another on the adaptive fitness landscape. However in his *Major Features of Evolution* (1953) Simpson wrote that it was still controversial "whether prospective adaptation as prelude to quantum evolution arises adaptively or inadaptively. It was concluded above that it usually arises adaptively . . . . The precise role of, say, genetic drift in this process thus is largely speculative at present. It may have an essential part or none. It surely is not involved in all cases of quantum evolution, but there is a strong possibility that it is often involved. If or when it is involved, it is an initiating mechanism. Drift can only rarely, and only for lower categories, have completed the transition to a new adaptive zone." (p. 390) This preference for adaptive over inadaptive forces lead Stephen Jay Gould to call attention to the "hardening of the Modern Synthesis" in the 1950s, where adaptationism took precedent over the pluralism of mechanisms common in the 1930s and 40s.

Simpson considered quantum evolution his crowning achievement, being "perhaps the most important outcome of [my] investigation, but also the most controversial and hypothetical." (1944, p. 206).

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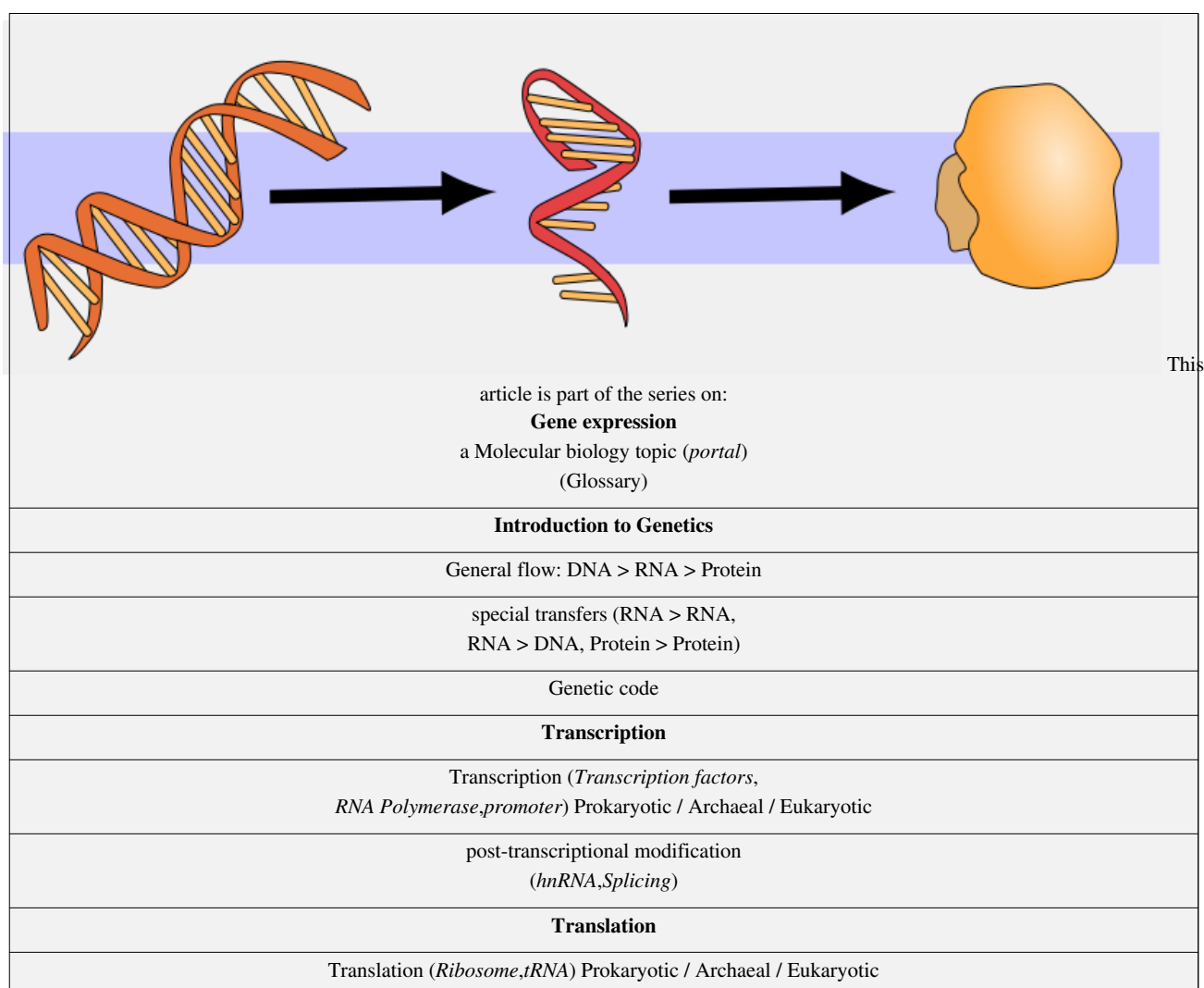
## External links

- George Gaylord Simpson <sup>[8]</sup> - Biographical sketch.
- Tempo and Mode in Evolution: Genetics and Paleontology 50 Years After Simpson <sup>[9]</sup>

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## Epigenetics



|                                                                                         |
|-----------------------------------------------------------------------------------------|
| post-translational modification<br>(functional groups, peptides,<br>structural changes) |
| <b>gene regulation</b>                                                                  |
| epigenetic regulation<br>(Genomic imprinting)                                           |
| transcriptional regulation                                                              |
| post-transcriptional regulation<br>(sequestration,<br>alternative splicing, miRNA)      |
| translational regulation                                                                |
| post-translational regulation<br>(reversible, irreversible)                             |
| ask a question <sup>[1]</sup> , edit <sup>[2]</sup>                                     |

In biology, the term **epigenetics** refers to changes in phenotype (appearance) or gene expression caused by mechanisms other than changes in the underlying DNA sequence, hence the name *epi-* (Greek: *επί*- over, above) *-genetics*. These changes may remain through cell divisions for the remainder of the cell's life and may also last for multiple generations. However, there is no change in the underlying DNA sequence of the organism;<sup>[3]</sup> instead, non-genetic factors cause the organism's genes to behave (or "express themselves") differently.<sup>[4]</sup>

The best example of epigenetic changes in eukaryotic biology is the process of cellular differentiation. During morphogenesis, totipotent stem cells become the various pluripotent cell lines of the embryo which in turn become fully differentiated cells. In other words, a single fertilized egg cell – the zygote – changes into the many cell types including neurons, muscle cells, epithelium, blood vessels etc. as it continues to divide. It does so by activating some genes while inhibiting others.<sup>[5]</sup>

## Etymology and definitions

According to Dr. Steve Folmar, the word *epigenetics* has had many definitions, and much of the confusion surrounding its usage relates to these definitions having changed over time. Initially it was used in a broader, less specific sense but it has become more narrowly linked to specific molecular phenomena occurring in organisms.<sup>[6]</sup>

*Epigenetics* (as in "epigenetic landscape") was coined by C. H. Waddington in 1942 as a portmanteau of the words *genetics* and *epigenesis*.<sup>[7]</sup> *Epigenesis* is an old<sup>[8]</sup> word which has more recently been used (see *preformationism* for historical background) to describe the differentiation of cells from their initial totipotent state in embryonic development. When Waddington coined the term the physical nature of genes and their role in heredity was not known; he used it as a conceptual model of how genes might interact with their surroundings to produce a phenotype.

Robin Holliday defined epigenetics as "the study of the mechanisms of temporal and spatial control of gene activity during the development of complex organisms."<sup>[9]</sup> Thus *epigenetic* can be used to describe anything other than DNA sequence that influences the development of an organism.

The modern usage of the word in scientific discourse is more narrow, referring to heritable traits (over rounds of cell division and sometimes transgenerationally) that do not involve changes to the underlying DNA sequence.<sup>[10]</sup> The Greek prefix *epi-* in *epigenetics* implies features that are "on top of" or "in addition to" genetics; thus *epigenetic* traits exist on top of or in addition to the traditional molecular basis for inheritance.

The similarity of the word to "genetics" has generated many parallel usages. The "epigenome" is a parallel to the word "genome," and refers to the overall epigenetic state of a cell. The phrase "genetic code" has also been



adapted—the "epigenetic code" has been used to describe the set of epigenetic features that create different phenotypes in different cells. Taken to its extreme, the "epigenetic code" could represent the total state of the cell, with the position of each molecule accounted for; more typically, the term is used in reference to systematic efforts to measure specific, relevant forms of epigenetic information such as the histone code or DNA methylation patterns.

*Epigenetic* was also used by the psychologist Erik Erikson in his Psychosocial development theory, however that usage is of primarily historical interest.<sup>[11]</sup>

Two predominant epigenetic mechanisms are DNA methylation and histone modification.

## Molecular basis of epigenetics

The molecular basis of epigenetics is complex. It involves modifications of the activation of certain genes, but not the basic structure of DNA. Additionally, the chromatin proteins associated with DNA may be activated or silenced. This accounts for why the differentiated cells in a multi-cellular organism express only the genes that are necessary for their own activity. Epigenetic changes are preserved when cells divide. Most epigenetic changes only occur within the course of one individual organism's lifetime, but, if a mutation in the DNA has been caused, some epigenetic changes are inherited from one generation to the next.<sup>[12]</sup> This raises the question of whether or not epigenetic changes in an organism can alter the basic structure of its DNA (see Evolution, below), a form of Lamarckism.

Specific epigenetic processes include paramutation, bookmarking, imprinting, gene silencing, X chromosome inactivation, position effect, reprogramming, transvection, maternal effects, the progress of carcinogenesis, many effects of teratogens, regulation of histone modifications and heterochromatin, and technical limitations affecting parthenogenesis and cloning.

Epigenetic research uses a wide range of molecular biologic techniques to further our understanding of epigenetic phenomena, including chromatin immunoprecipitation (together with its large-scale variants ChIP-on-chip and ChIP-seq), fluorescent in situ hybridization, methylation-sensitive restriction enzymes, DNA adenine methyltransferase identification (DamID) and bisulfite sequencing. Furthermore, the use of bioinformatic methods is playing an increasing role (computational epigenetics).

## Mechanisms

Several types of epigenetic inheritance systems may play a role in what has become known as cell memory:<sup>[13]</sup>

### DNA methylation and chromatin remodeling

Because the phenotype of a cell or individual is affected by which of its genes are transcribed, heritable transcription states can give rise to epigenetic effects. There are several layers of regulation of gene expression. One way that genes are regulated is through the remodeling of chromatin. Chromatin is the complex of DNA and the histone proteins with which it associates. Histone proteins are little spheres that DNA wraps around. If the way that DNA is wrapped around the histones changes, gene expression can change as well. Chromatin remodeling is accomplished through two main mechanisms:

1. The first way is post translational modification of the amino acids that make up histone proteins. Histone proteins are made up of long chains of amino acids. If the amino acids that are in the chain are changed, the shape of the histone sphere might be modified. DNA is not completely unwound during replication. It is possible, then, that the modified histones may be carried into each new copy of the DNA. Once there, these histones may act as templates, initiating the surrounding new histones to be shaped in the new manner. By altering the shape of the histones around it, these modified histones would ensure that a differentiated cell would stay differentiated, and not convert back into being a stem cell.
2. The second way is the addition of methyl groups to the DNA, mostly at CpG sites, to convert cytosine to 5-methylcytosine. 5-Methylcytosine performs much like a regular cytosine, pairing up with a G, so in the next round of cell division it will be replaced with a regular C. However, some areas of genome are methylated heavier than others and highly methylated areas tend to be transcriptionally less active, through a mechanism not fully understood. Methylation of cytosines can also persist from the germ line of one of the parents into the zygote, marking the chromosome as being inherited from this parent (genetic imprinting).

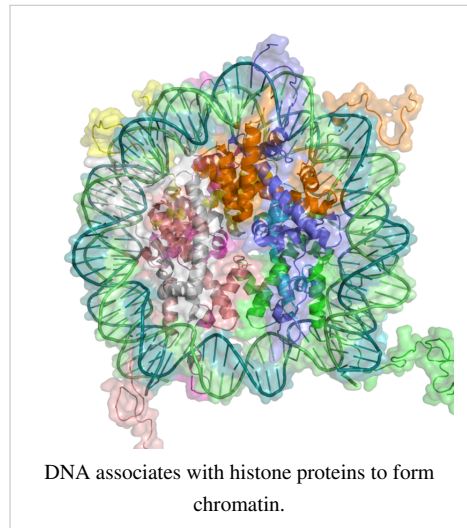
The way that the cells stay differentiated in the case of DNA methylation is clearer to us than it is in the case of histone shape. Basically, certain enzymes (such as DNMT1) have a higher affinity for the methylated cytosine. If this enzyme reaches a "hemimethylated" portion of DNA (where methylcytosine is in only one of the two DNA strands) the enzyme will methylate the other half.

Although histone modifications occur throughout the entire sequence, the unstructured N-termini of histones (called histone tails) are particularly highly modified. These modifications include acetylation, methylation, ubiquitylation, phosphorylation and sumoylation. Acetylation is the most highly studied of these modifications. For example, acetylation of the K14 and K9 lysines of the tail of histone H3 by histone acetyltransferase enzymes (HATs) is generally correlated with transcriptional competence.

One mode of thinking is that this tendency of acetylation to be associated with "active" transcription is biophysical in nature. Because it normally has a positively charged nitrogen at its end, lysine can bind the negatively charged phosphates of the DNA backbone and prevent them from repelling each other. The acetylation event converts the positively charged amine group on the side chain into a neutral amide linkage. This removes the positive charge, causing the DNA to repel itself. When this occurs, complexes like SWI/SNF and other transcriptional factors can bind to the DNA, thus opening it up and exposing it to enzymes like RNA polymerase so transcription of the gene can occur.

In addition, the positively charged tails of histone proteins from one nucleosome may interact with the histone proteins on a neighboring nucleosome, causing them to pack closely. Lysine acetylation may interfere with these interactions, causing the chromatin structure to open up.

Lysine acetylation may also act as a beacon to recruit other activating chromatin modifying enzymes (and basal transcription machinery as well). Indeed, the bromodomain — a protein segment (domain) that specifically binds



acetyl-lysine — is found in many enzymes that help activate transcription, including the SWI/SNF complex (on the protein polybromo). It may be that acetylation acts in this and the previous way to aid in transcriptional activation.

The idea that modifications act as docking modules for related factors is borne out by histone methylation as well. Methylation of lysine 9 of histone H3 has long been associated with constitutively transcriptionally silent chromatin (constitutive heterochromatin). It has been determined that a chromodomain (a domain that specifically binds methyl-lysine) in the transcriptionally repressive protein HP1 recruits HP1 to K9 methylated regions. One example that seems to refute this biophysical model for acetylation is that tri-methylation of histone H3 at lysine 4 is strongly associated with (and required for full) transcriptional activation. Tri-methylation in this case would introduce a fixed positive charge on the tail.

It should be emphasized that differing histone modifications are likely to function in differing ways; acetylation at one position is likely to function differently than acetylation at another position. Also, multiple modifications may occur at the same time, and these modifications may work together to change the behavior of the nucleosome. The idea that multiple dynamic modifications regulate gene transcription in a systematic and reproducible way is called the histone code.

DNA methylation frequently occurs in repeated sequences, and helps to suppress the expression and mobility of 'transposable elements'.<sup>[14]</sup> Because 5-methylcytosine is chemically very similar to thymidine, CpG sites are frequently mutated and become rare in the genome, except at CpG islands where they remain unmethylated. Epigenetic changes of this type thus have the potential to direct increased frequencies of permanent genetic mutation. DNA methylation patterns are known to be established and modified in response to environmental factors by a complex interplay of at least three independent DNA methyltransferases, DNMT1, DNMT3A and DNMT3B, the loss of any of which is lethal in mice.<sup>[15]</sup> DNMT1 is the most abundant methyltransferase in somatic cells,<sup>[16]</sup> localizes to replication foci,<sup>[17]</sup> has a 10–40-fold preference for hemimethylated DNA and interacts with the proliferating cell nuclear antigen (PCNA).<sup>[18]</sup> By preferentially modifying hemimethylated DNA, DNMT1 transfers patterns of methylation to a newly synthesized strand after DNA replication, and therefore is often referred to as the 'maintenance' methyltransferase.<sup>[19]</sup> DNMT1 is essential for proper embryonic development, imprinting and X-inactivation.<sup>[15] [20]</sup>

Chromosomal regions can adopt stable and heritable alternative states resulting in bistable gene expression without changes to the DNA sequence. Epigenetic control is often associated with alternative covalent modifications of histones. The stability and heritability of states of larger chromosomal regions are often thought to involve positive feedback where modified nucleosomes recruit enzymes that similarly modify nearby nucleosomes. A simplified stochastic model for this type of epigenetics is found here <sup>[21] [22]</sup>.

Because DNA methylation and chromatin remodeling play such a central role in many types of epigenetic inheritance, the word "epigenetics" is sometimes used as a synonym for these processes. However, this can be misleading. Chromatin remodeling is not always inherited, and not all epigenetic inheritance involves chromatin remodeling.<sup>[23]</sup>

It has been suggested that the histone code could be mediated by the effect of small RNAs. The recent discovery and characterization of a vast array of small (21- to 26-nt), non-coding RNAs suggests that there is an RNA component, possibly involved in epigenetic gene regulation. Small interfering RNAs can modulate transcriptional gene expression via epigenetic modulation of targeted promoters.<sup>[24]</sup>

## RNA transcripts and their encoded proteins

Sometimes a gene, after being turned on, transcribes a product that (either directly or indirectly) maintains the activity of that gene. For example, Hnf4 and MyoD enhance the transcription of many liver- and muscle-specific genes, respectively, including their own, through the transcription factor activity of the proteins they encode. RNA signalling includes differential recruitment of a hierarchy of generic chromatin modifying complexes and DNA methyltransferases to specific loci by RNAs during differentiation and development<sup>[25]</sup>. Other epigenetic changes are mediated by the production of different splice forms of RNA, or by formation of double-stranded RNA (RNAi).

Descendants of the cell in which the gene was turned on will inherit this activity, even if the original stimulus for gene-activation is no longer present. These genes are most often turned on or off by signal transduction, although in some systems where syncytia or gap junctions are important, RNA may spread directly to other cells or nuclei by diffusion. A large amount of RNA and protein is contributed to the zygote by the mother during oogenesis or via nurse cells, resulting in maternal effect phenotypes. A smaller quantity of sperm RNA is transmitted from the father, but there is recent evidence that this epigenetic information can lead to visible changes in several generations of offspring.<sup>[26]</sup>

## Prions

Prions are infectious forms of proteins. Proteins generally fold into discrete units which perform distinct cellular functions, but some proteins are also capable of forming an infectious conformational state known as a prion. Although often viewed in the context of infectious disease, prions are more loosely defined by their ability to catalytically convert other native state versions of the same protein to an infectious conformational state. It is in this latter sense that they can be viewed as epigenetic agents capable of inducing a phenotypic change without a modification of the genome.<sup>[27]</sup>

Fungal prions are considered epigenetic because the infectious phenotype caused by the prion can be inherited without modification of the genome. PSI<sup>+</sup> and URE3, discovered in yeast in 1965 and 1971, are the two best studied of this type of prion.<sup>[28] [29]</sup> Prions can have a phenotypic effect through the sequestration of protein in aggregates, thereby reducing that protein's activity. In PSI<sup>+</sup> cells, the loss of the Sup35 protein (which is involved in termination of translation) causes ribosomes to have a higher rate of read-through of stop codons, an effect which results in suppression of nonsense mutations in other genes.<sup>[30]</sup> The ability of Sup35 to form prions may be a conserved trait. It could confer an adaptive advantage by giving cells the ability to switch into a PSI<sup>+</sup> state and express dormant genetic features normally terminated by premature stop codon mutations.<sup>[31] [32]</sup>

## Structural inheritance systems

In ciliates such as *Tetrahymena* and *Paramecium*, genetically identical cells show heritable differences in the patterns of ciliary rows on their cell surface. Experimentally altered patterns can be transmitted to daughter cells. It seems existing structures act as templates for new structures. The mechanisms of such inheritance are unclear, but reasons exist to assume that multicellular organisms also use existing cell structures to assemble new ones.<sup>[33]</sup>

## Functions and consequences

### Development

Somatic epigenetic inheritance, particularly through DNA methylation and chromatin remodeling, is very important in the development of multicellular eukaryotic organisms. The genome sequence is static (with some notable exceptions), but cells differentiate in many different types, which perform different functions, and respond differently to the environment and intercellular signalling. Thus, as individuals develop, morphogens activate or silence genes in an epigenetically heritable fashion, giving cells a "memory". In mammals, most cells terminally differentiate, with only stem cells retaining the ability to differentiate into several cell types ("totipotency" and "multipotency"). In mammals, some stem cells continue producing new differentiated cells throughout life, but mammals are not able to respond to loss of some tissues, for example, the inability to regenerate limbs, which some other animals are capable of. Unlike animals, plant cells do not terminally differentiate, remaining totipotent with the ability to give rise to a new individual plant. While plants do utilise many of the same epigenetic mechanisms as animals, such as chromatin remodeling, it has been hypothesised that plant cells do not have "memories", resetting their gene expression patterns at each cell division using positional information from the environment and surrounding cells to determine their fate.<sup>[34]</sup>

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## Medicine

Epigenetics has many and varied potential medical applications. Congenital genetic disease is well understood, and it is also clear that epigenetics can play a role, for example, in the case of Angelman syndrome and Prader-Willi syndrome. These are normal genetic diseases caused by gene deletions or inactivation of the genes, but are unusually common because individuals are essentially hemizygous because of genomic imprinting, and therefore a single gene knock out is sufficient to cause the disease, where most cases would require both copies to be knocked out.<sup>[35]</sup>

## Evolution

Although epigenetics in multicellular organisms is generally thought to be a mechanism involved in differentiation, with epigenetic patterns "reset" when organisms reproduce, there have been some observations of transgenerational epigenetic inheritance (e.g., the phenomenon of paramutation observed in maize). Although most of these multigenerational epigenetic traits are gradually lost over several generations, the possibility remains that multigenerational epigenetics could be another aspect to evolution and adaptation. These effects may require enhancements to the standard conceptual framework of the modern evolutionary synthesis.<sup>[36] [37]</sup>

Epigenetic features may play a role in short-term adaptation of species by allowing for reversible phenotype variability. The modification of epigenetic features associated with a region of DNA allows organisms, on a multigenerational time scale, to switch between phenotypes that express and repress that particular gene.<sup>[38]</sup> When the DNA sequence of the region is not mutated, this change is reversible. It has also been speculated that organisms may take advantage of differential mutation rates associated with epigenetic features to control the mutation rates of particular genes.<sup>[38]</sup>

Epigenetic changes have also been observed to occur in response to environmental exposure—for example, mice given some dietary supplements have epigenetic changes affecting expression of the agouti gene, which affects their fur color, weight, and propensity to develop cancer.<sup>[39] [40]</sup>

## Transgenerational epigenetic observations

A comprehensive review of over 100 cases of transgenerational epigenetic inheritance reported the phenomena in a wide range of organisms including prokaryotes, plants, and animals.<sup>[41]</sup>

## Epigenetic effects in humans

### Genomic imprinting and related disorders

Some human disorders are associated with genomic imprinting, a phenomenon in mammals where the father and mother contribute different epigenetic patterns for specific genomic loci in their germ cells.<sup>[42]</sup> The best-known case of imprinting in human disorders is that of Angelman syndrome and Prader-Willi syndrome—both can be produced by the same genetic mutation, chromosome 15q partial deletion, and the particular syndrome that will develop depends on whether the mutation is inherited from the child's mother or from their father.<sup>[43]</sup> This is due to the presence of genomic imprinting in the region. Beckwith-Wiedemann syndrome is also associated with genomic imprinting, often caused by abnormalities in maternal genomic imprinting of a region on chromosome 11.

### Transgenerational epigenetic observations

Marcus Pembrey and colleagues also observed that the paternal (but not maternal) grandsons of Swedish boys who were exposed during preadolescence to famine in the 19th century were less likely to die of cardiovascular disease; if food was plentiful then diabetes mortality in the grandchildren increased, suggesting that this was a transgenerational epigenetic inheritance.<sup>[44]</sup> The opposite effect was observed for females -- the paternal (but not maternal) granddaughters of women who experienced famine while in the womb (and their eggs were being formed) lived

shorter lives on average.<sup>[45]</sup>

### Cancer and developmental abnormalities

A variety of compounds are considered as epigenetic carcinogens—they result in an increased incidence of tumors, but they do not show mutagen activity (toxic compounds or pathogens that cause tumors incident to increased regeneration should also be excluded). Examples include diethylstilbestrol, arsenite, hexachlorobenzene, and nickel compounds.

Many teratogens exert specific effects on the fetus by epigenetic mechanisms.<sup>[46] [47]</sup> While epigenetic effects may preserve the effect of a teratogen such as diethylstilbestrol throughout the life of an affected child, the possibility of birth defects resulting from exposure of fathers or in second and succeeding generations of offspring has generally been rejected on theoretical grounds and for lack of evidence.<sup>[48]</sup> However, a range of male-mediated abnormalities have been demonstrated, and more are likely to exist.<sup>[49]</sup> FDA label information<sup>[50]</sup> for Vidaza(tm), a formulation of 5-azacitidine (an unmethylatable analog of cytidine that causes hypomethylation when incorporated into DNA) states that "men should be advised not to father a child" while using the drug, citing evidence in treated male mice of reduced fertility, increased embryo loss, and abnormal embryo development. In rats, endocrine differences were observed in offspring of males exposed to morphine.<sup>[51]</sup> In mice, second generation effects of diethylstilbestrol have been described occurring by epigenetic mechanisms.<sup>[52]</sup> In 2008, the National Institutes of Health announced that \$190 million had been earmarked for epigenetics research over the next five years. In announcing the funding, government officials noted that epigenetics has the potential to explain mechanisms of aging, human development, and the origins of cancer, heart disease, mental illness, as well as several other conditions. Some investigators, like Randy Jirtle, PhD, of Duke University Medical Center, think epigenetics may ultimately turn out to have a greater role in disease than genetics.<sup>[53]</sup>

### Twin studies

Recent studies involving both dizygotic and monozygotic twins have produced some evidence of epigenetic influence in humans.<sup>[54] [55] [56]</sup>

### Epigenetics in microorganisms

Bacteria make widespread use of postreplicative DNA methylation for the epigenetic control of DNA-protein interactions. Bacteria make use of DNA adenine methylation (rather than DNA cytosine methylation) as an epigenetic signal. DNA adenine methylation is important in bacteria virulence in organisms such as *Escherichia coli*, *Salmonella*, *Vibrio*, *Yersinia*, *Haemophilus*, and *Brucella*. In *Alphaproteobacteria*, methylation of adenine regulates the cell cycle and couples gene transcription to DNA replication. In *Gammaproteobacteria*, adenine methylation provides signals for DNA replication, chromosome segregation, mismatch repair, packaging of bacteriophage, transposase activity and regulation of gene expression.<sup>[57] [58]</sup>

The yeast prion PSI is generated by a conformational change of a translation termination factor, which is then inherited by daughter cells. This can provide a survival advantage under adverse conditions. This is an example of epigenetic regulation enabling unicellular organisms to respond rapidly to environmental stress. Prions can be viewed as epigenetic agents capable of inducing a phenotypic change without modification of the genome.<sup>[58]</sup>

## See also

- Epigenetic Theory
- Baldwinian evolution
- Centromere
- Computational epigenetics
- Dutch famine of 1944 (scientific legacy)
- Evolutionary developmental psychology
- Histone code
- Molecular biology
- Somatic epitype
- Synthetic genetic array
- Weismann barrier

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## External links

- DNA Is Not Destiny <sup>[72]</sup> - Discover Magazine cover story
- BBC - Horizon - 2005 - The Ghost In Your Genes <sup>[73]</sup>
- Epigenetics article <sup>[74]</sup> at Hopkins Medicine

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- [8] According to the Oxford English Dictionary:  
The word is used by W. Harvey, *Exercitationes* 1651, p. 148, and in the *English Anatomical Exercitationes* 1653, p. 272. It is explained to mean 'partium super-exorientium additamentum', 'the additament of parts budding one out of another'.  
It is also worth quoting this adumbration of the definition given there (viz., "The formation of an organic germ as a new product"):  
**theory of epigenesis:** the theory that the germ is brought into existence (by successive accretions), and not merely developed, in the process of reproduction. [...] The opposite theory was formerly known as the 'theory of evolution'; to avoid the ambiguity of this name, it is now spoken of chiefly as the 'theory of preformation', sometimes as that of 'encasement' or 'emboîtement'.
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## Epigenetic landscape

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**Epigenetic landscape** is a metaphor for biological development. Its originator, Conrad Hal Waddington, said that cell fates were established in development much like a marble rolls down to the point of lowest local elevation. Waddington suggested visualising increasing irreversibility of cell type differentiation as ridges rising between the valleys where the marbles (cells) are travelling.

Today, the term refers to the combined epigenetic modifications of a given domain of DNA sequence. Epigenetic modifications include methylation of cytosine residues of DNA and post-translational modifications of the histone proteins associated with the DNA strand. The specific combination of epigenetic modifications determines the conformation of the chromatin fibre into which the DNA and histones are packaged, and can thereby regulate the transcriptional potential of the underlying genes.

### See also

- Epigenetics

## Epigenetic Theory

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*Not to be confused with Epigenetics, which refers to partially heritable biological changes affecting gene expression, or with Epigenesis (biology), which is a widely accepted theory of cell differentiation for multicellular organisms.*

**Epigenetic theory** is an emergent theory of development that includes both the genetic origins of behavior and the direct systematic influence that environmental forces have, over time, on the expression of those genes. The theory focuses on the dynamic interaction between these two influences during development.

Interactivist ideas of development has been discussed in various forms and under various names throughout the 19th and 20th centuries. An early version was proposed, among the founding statements in embryology, by Karl Ernst von Baer and popularized by Ernst Haeckel. A different approach, James Mark Baldwin's "Baldwin effect," is prominent in contemporary discourses. Remarkably, however, its update by Jean Piaget is rarely discussed. A radical epigenetic view (physiological epigenesis) was developed by Paul Wintrebert. Another variation, probabilistic epigenesis, was presented by Gilbert Gottlieb in 2003.

### See also

- Nature vs. nurture
  - preformism
  - evo-devo
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# Evolutionary developmental biology

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**Evolutionary developmental biology** (**evolution of development** or informally, **evo-devo**) is a field of biology that compares the developmental processes of different animals and plants in an attempt to determine the ancestral relationship between organisms and how developmental processes evolved. It addresses the origin and evolution of embryonic development; how modifications of development and developmental processes lead to the production of novel features, such as the evolution of feathers<sup>[1]</sup>; the role of developmental plasticity in evolution; how ecology impacts in development and evolutionary change; and the developmental basis of homoplasy and homology.<sup>[2]</sup>

Although interest in the relationship between ontogeny and phylogeny extends back to the nineteenth century, the contemporary field of evo-devo has gained impetus from the discovery of genes regulating embryonic development in model organisms. General hypotheses remain hard to test because organisms differ so much in shape and form.<sup>[3]</sup> Nevertheless, it now appears that just as evolution tends to create new genes from parts of old genes (molecular economy), evo-devo demonstrates that evolution alters developmental processes (genes and gene networks) to create new and novel structures from the old gene networks (such as bone structures of the jaw deviating to the ossicles of the middle ear) or will conserve (molecular economy) a similar program in a host of organisms such as eye development genes in molluscs, insects, and vertebrates<sup>[4] [5]</sup>. Initially the major interest has been in the evidence of homology in the cellular and molecular mechanisms that regulate body plan and organ development. However more modern approaches include developmental changes associated with speciation.<sup>[6]</sup>

## Basic principles

Charles Darwin's theory of evolution is based on three principles: natural selection, heredity, and variation. At the time that Darwin wrote, the principles underlying heredity and variation were poorly understood. In the 1940s, however, biologists incorporated Gregor Mendel's principles of genetics to explain both, resulting in the modern synthesis. It was not until the 1980s and 1990s, however, when more comparative molecular sequence data between different kinds of organisms was amassed and detailed, that an understanding of the molecular basis of the developmental mechanisms has arisen. Currently, it is well understood how genetic mutation occurs. However, developmental mechanisms are not understood sufficiently to explain which kinds of phenotypic variation can arise in each generation from variation at the genetic level. Evolutionary developmental biology studies how the dynamics of development determine the phenotypic variation arising from genetic variation and how that affects phenotypic evolution (specially its direction). At the same time evolutionary developmental biology also studies how development itself evolves. Thus, the origins of evolutionary developmental biology come from both an improvement in molecular biology techniques as applied to development, and the full appreciation of the limitations of classic neo-Darwinism as applied to phenotypic evolution. Some evo-devo researchers see themselves as extending and enhancing the modern synthesis by incorporating into it findings of molecular genetics and developmental biology. Others, drawing on findings of discordances between genotype and phenotype and epigenetic mechanisms of development, are mounting an explicit challenge to neo-Darwinism.

Evolutionary developmental biology is not yet a unified discipline, but can be distinguished from earlier approaches to evolutionary theory by its focus on a few crucial ideas. One of these is modularity: as has been long recognized, plants and animal bodies are modular: they are organized into developmentally and anatomically distinct parts. Often these parts are repeated, such as fingers, ribs, and body segments. Evo-devo seeks the genetic and evolutionary basis for the division of the embryo into distinct modules, and for the partly independent development of such modules.

Another central idea is that some gene products function as switches whereas others act as diffusible signals. Genes specify proteins, some of which act as structural components of cells and others as enzymes that regulate various biochemical pathways within an organism. Most biologists working within the modern synthesis assumed that an organism is a straightforward reflection of its component genes. The modification of existing, or evolution of new, biochemical pathways (and, ultimately, the evolution of new species of organisms) depended on specific genetic

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mutations. In 1961, however, Jacques Monod, Jean-Pierre Changeux and François Jacob discovered within the bacterium *Escherichia coli* a gene that functioned only when "switched on" by an environmental stimulus.<sup>[7]</sup> Later, scientists discovered specific genes in animals, including a subgroup of the genes which contain the homeobox DNA motif, called Hox genes, that act as switches for other genes, and could be induced by other gene products, morphogens, that act analogously to the external stimuli in bacteria. These discoveries drew biologists' attention to the fact that genes can be selectively turned on and off, rather than being always active, and that highly disparate organisms (for example, fruit flies and human beings) may use the same genes for embryogenesis (e.g., the genes of the "developmental-genetic toolkit", see below), just regulating them differently.

Similarly, organismal form can be influenced by mutations in promoter regions of genes, those DNA sequences at which the products of some genes bind to and control the activity of the same or other genes, not only protein-specifying sequences. In addition to providing new support for Darwin's assertion that all organisms are descended from a common ancestor, this finding suggested that the crucial distinction between different species (even different orders or phyla) may be due less to differences in their content of gene products than to differences in spatial and temporal *expression* of conserved genes. The implication that large evolutionary changes in body morphology are associated with changes in gene regulation, rather than the evolution of new genes, suggested that the action of natural selection on promoters responsive to Hox and other "switch" genes may play a major role in evolution.

Another focus of evo-devo is developmental plasticity, the basis of the recognition that organismal phenotypes are not uniquely determined by their genotypes. If generation of phenotypes is conditional, and dependent on external or environmental inputs, evolution can proceed by a "phenotype-first" route,<sup>[8] [3]</sup> with genetic change following, rather than initiating, the formation of morphological and other phenotypic novelties. The case for this was argued for by Mary Jane West-Eberhard in her 2003 book *Developmental plasticity and evolution*.<sup>[8]</sup>

## History

An early version of recapitulation theory, also called the *biogenetic law* or *embryological parallelism*, was put forward by Étienne Serres in 1824–26 as what became known as the "Meckel-Serres Law" which attempted to provide a link between comparative embryology and a "pattern of unification" in the organic world. It was supported by Étienne Geoffroy Saint-Hilaire as part of his ideas of idealism, and became a prominent part of his version of Lamarckism leading to disagreements with Georges Cuvier. It was widely supported in the Edinburgh and London schools of higher anatomy around 1830, notably by Robert Edmond Grant, but was opposed by Karl Ernst von Baer's embryology of divergence in which embryonic parallels only applied to early stages where the embryo took a general form, after which more specialised forms diverged from this shared unity in a branching pattern. The anatomist Richard Owen used this to support his idealist concept of species as showing the unrolling of a divine plan from an archetype, and in the 1830s attacked the transmutation of species proposed by Lamarck, Geoffroy and Grant.<sup>[9]</sup> In the 1850s Owen began to support an evolutionary view that the history of life was the gradual unfolding of a teleological divine plan,<sup>[10]</sup> in a continuous "ordained becoming", with new species appearing by natural birth.<sup>[11]</sup>

In *On the Origin of Species* (1859), Charles Darwin proposed evolution through natural selection, a theory central to modern biology. Darwin recognised the importance of embryonic development in the understanding of evolution, and the way in which von Baer's branching pattern matched his own idea of descent with modification<sup>[12]</sup>:

“We can see why characters derived from the embryo should be of equal importance with those derived from the adult, for a natural classification of course includes all ages.”<sup>[13]</sup>

Ernst Haeckel (1866), in his endeavour to produce a synthesis of Darwin's theory with Lamarckism and Naturphilosophie, proposed that "ontogeny recapitulates phylogeny," that is, the development of the embryo of every species (ontogeny) fully repeats the evolutionary development of that species (phylogeny), in Geoffroy's linear

model rather than Darwin's idea of branching evolution.<sup>[12]</sup> Haeckel's concept explained, for example, why humans, and indeed all vertebrates, have gill slits and tails early in embryonic development. His theory has since been discredited. However, it served as a backdrop for a renewed interest in the evolution of development after the modern evolutionary synthesis was established (roughly 1936 to 1947).

Stephen Jay Gould called this approach to explaining evolution as *terminal addition*; as if every evolutionary advance was added as new stage by reducing the duration of the older stages. The idea was based on observations of neoteny.<sup>[14]</sup> This was extended by the more general idea of heterochrony (changes in timing of development) as a mechanism for evolutionary change;<sup>[15]</sup>

D'Arcy Thompson postulated that differential growth rates could produce variations in form in his 1917 book *On Growth and Form*. He showed the underlying similarities in *body plans* and how geometric *transformations* could be used to explain the variations.

Edward B. Lewis discovered homeotic genes, rooting the emerging discipline of evo-devo in molecular genetics. In 2000, a special section of the Proceedings of the National Academy of Sciences (PNAS) was devoted to "evo-devo",<sup>[16]</sup> and an entire 2005 issue of the Journal of Experimental Zoology Part B: Molecular and Developmental Evolution was devoted to the key evo-devo topics of evolutionary innovation and morphological novelty.<sup>[17]</sup>

## The developmental-genetic toolkit

**The developmental-genetic toolkit** consists of genes whose products control the development of a multicellular organism. Differences in deployment of toolkit genes affect the body plan and the number, identity, and pattern of body parts. The toolkit is highly conserved across animal phyla. Only a small fraction of the genes in the genome are involved in development. The majority of toolkit genes are components of signaling pathways, and encode for the production of transcription factors, cell adhesion proteins, cell surface receptor proteins, and secreted morphogens. Their function is highly correlated with their spatial and temporal expression patterns. One of the major goals of evo-devo is to catalogue all genes (their identity, product, function, and interaction) in the toolkit.

Among the most important of the toolkit genes are those of the **Hox** gene cluster, or complex. Hox genes, transcription factors containing the more broadly distributed homeobox protein-binding DNA motif, function in patterning the body axis. Thus, by combinatorially specifying the identity of particular body regions, Hox genes determine where limbs and other body segments will grow in a developing embryo or larva. Mutations in any one of these genes can lead to the growth of extra, typically non-functional body parts in invertebrates, for example aristapedia complex in *Drosophila*, which results in a leg growing from the head in place of an antenna and is due to a defect in a single gene (this mutation is also known as Antennapedia). Another example is the expansion of *Hoxc8* and *Hoxc6* expression in snakes, where they are expressed all the way to the head rather than just the thoracic region, preventing the development of forelimbs.<sup>[18]</sup>

## Development and the origin of novelty

Among the more surprising and, perhaps, counterintuitive (from a neo-Darwinian viewpoint) results of recent research in evolutionary developmental biology is that the diversity of body plans and morphology in organisms across many phyla are not necessarily reflected in diversity at the level of the sequences of genes, including those of the developmental genetic toolkit and other genes involved in development. Indeed, as Gerhart and Kirschner have noted, there is an apparent paradox: "where we most expect to find variation, we find conservation, a lack of change".<sup>[19]</sup>

Even within a species, the occurrence of novel forms within a population does not generally correlate with levels of genetic variation sufficient to account for all morphological diversity. For example, there is significant variation in limb morphologies amongst salamanders and in differences in segment number in centipedes, even when the

respective genetic variation is low.

A major question then, for evo-devo studies, is: If the morphological novelty we observe at the level of different clades is not always reflected in the genome, where does it come from? Apart from neo-Darwinian mechanisms such as mutation, translocation and duplication of genes, novelty may also arise by mutation-driven changes in gene regulation. The finding that much biodiversity is not due to differences in genes, but rather to alterations in gene regulation, has introduced an important new element into evolutionary theory.<sup>[20]</sup> Diverse organisms may have highly conserved developmental genes, but highly divergent regulatory mechanisms for these genes. Changes in gene regulation are "second-order" effects of genes, resulting from the interaction and timing of activity of gene networks, as distinct from the functioning of the individual genes in the network.

The discovery of the homeotic Hox gene family in vertebrates in the 1980s allowed researchers in developmental biology to empirically assess the relative roles of gene duplication and gene regulation with respect to their importance in the evolution of morphological diversity. Several biologists, including Sean B. Carroll of the University of Wisconsin–Madison suggest that "changes in the cis-regulatory systems of genes" are more significant than "changes in gene number or protein function".<sup>[21]</sup> These researchers argue that the combinatorial nature of transcriptional regulation allows a rich substrate for morphological diversity, since variations in the level, pattern, or timing of gene expression may provide more variation for natural selection to act upon than changes in the gene product alone.

Epigenetic alterations of gene regulation or phenotype generation that are subsequently consolidated by changes at the gene level constitute another class of mechanisms for evolutionary innovation. Epigenetic changes include modification of the genetic material due to methylation and other reversible chemical alteration <sup>[22]</sup>, as well as nonprogrammed remolding of the organism by physical and other environmental effects due to the inherent plasticity of developmental mechanisms.<sup>[8]</sup> The biologists Stuart A. Newman and Gerd B. Müller have suggested that organisms early in the history of multicellular life were more susceptible to this second category of epigenetic determination than are modern organisms, providing a basis for early macroevolutionary changes.<sup>[23]</sup>

## See also

- Developmental biology
  - Animal evolution
  - Plant Evolutionary Developmental Biology
  - Baldwin effect
  - Developmental systems theory
  - Evolution of multicellularity
  - Genetic assimilation
  - Ontogeny
  - Ontogeny recapitulates phylogeny
  - List of gene families
  - Important publications in evolutionary developmental biology
  - Evolution and Development Leading journal
  - Body plan
  - Cell signaling
  - Signal transduction
  - Cell signaling networks
  - Transcription factor
  - Enhancer
  - Enhanceosome
  - Promoter
-

- Gene regulatory network

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## External links

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- Tardigrades (water bears) as evo-devo models, a short video from NPR's Science Friday<sup>[39]</sup>

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# Catastrophe theory

*This article is about the study of dynamical systems. For other meanings, see catastrophe.*

In mathematics, **catastrophe theory** is a branch of bifurcation theory in the study of dynamical systems; it is also a particular special case of more general singularity theory in geometry.

Bifurcation theory studies and classifies phenomena characterized by sudden shifts in behavior arising from small changes in circumstances, analysing how the qualitative nature of equation solutions depends on the parameters that appear in the equation. This may lead to sudden and dramatic changes, for example the unpredictable timing and magnitude of a landslide.

Catastrophe theory, which originated with the work of the French mathematician René Thom in the 1960s, and became very popular due to the efforts of Christopher Zeeman in the 1970s, considers the special case where the long-run stable equilibrium can be identified with the minimum of a smooth, well-defined potential function (Lyapunov function).

Small changes in certain parameters of a nonlinear system can cause equilibria to appear or disappear, or to change from attracting to repelling and vice versa, leading to large and sudden changes of the behaviour of the system. However, examined in a larger parameter space, catastrophe theory reveals that such bifurcation points tend to occur as part of well-defined qualitative geometrical structures.

## Elementary catastrophes

Catastrophe theory analyses *degenerate critical points* of the potential function — points where not just the first derivative, but one or more higher derivatives of the potential function are also zero. These are called the germs of the catastrophe geometries. The degeneracy of these critical points can be *unfolded* by expanding the potential function as a Taylor series in small perturbations of the parameters.

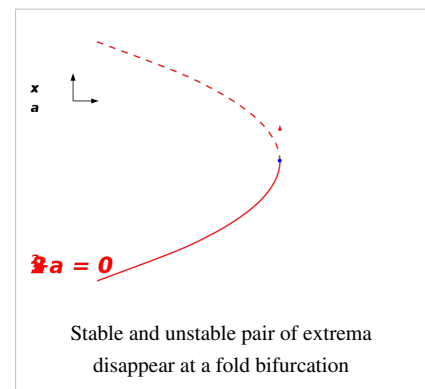
When the degenerate points are not merely accidental, but are structurally stable, the degenerate points exist as organising centres for particular geometric structures of lower degeneracy, with critical features in the parameter space around them. If the potential function depends on two or fewer active variables, and four (resp. five) or fewer active parameters, then there are only seven (resp. eleven) generic structures for these bifurcation geometries, with corresponding standard forms into which the Taylor series around the catastrophe germs can be transformed by diffeomorphism (a smooth transformation whose inverse is also smooth). These seven fundamental types are now presented, with the names that Thom gave them.

## Potential functions of one active variable

### Fold catastrophe

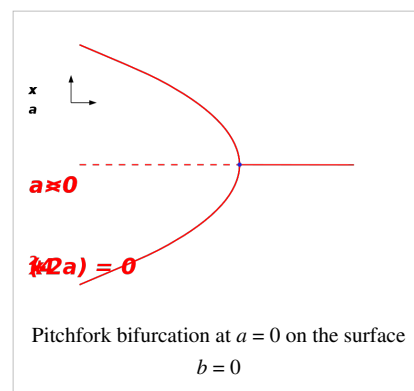
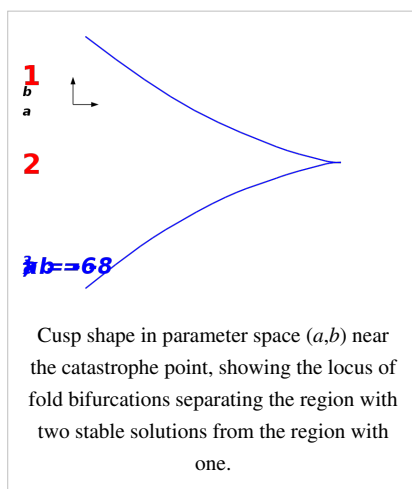
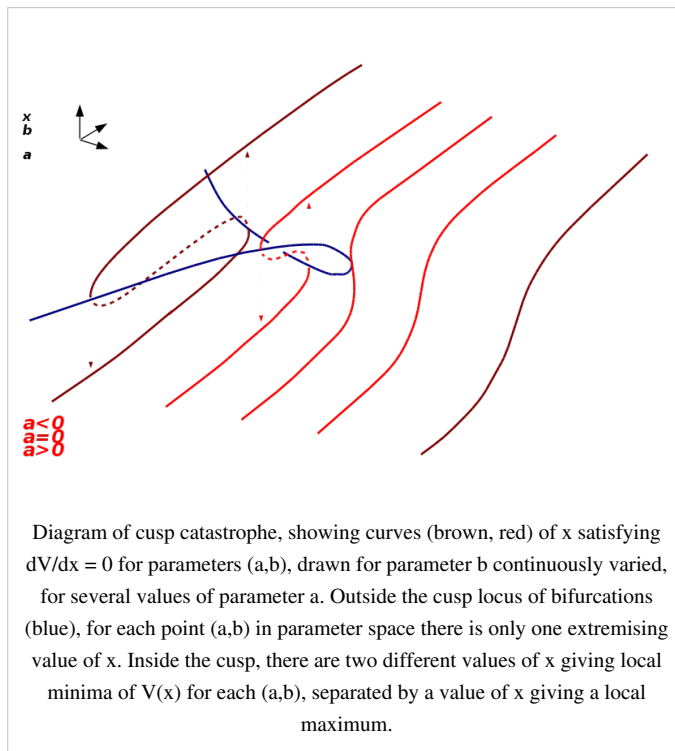
$$V = x^3 + ax$$

At negative values of  $a$ , the potential has two extrema - one stable, and one unstable. If the parameter  $a$  is slowly increased, the system can follow the stable minimum point. But at  $a = 0$  the stable and unstable extrema meet, and annihilate. This is the bifurcation point. At  $a > 0$  there is no longer a stable solution. If a physical system is followed through a fold bifurcation, one therefore finds that as  $a$  reaches 0, the stability of the  $a < 0$  solution is suddenly lost, and the system will make a sudden transition to a new, very different behaviour. This bifurcation value of the parameter  $a$  is sometimes called the tipping point.



## Cusp catastrophe

$$V = x^4 + ax^2 + bx$$



The cusp geometry is very common, when one explores what happens to a fold bifurcation if a second parameter,  $b$ , is added to the control space. Varying the parameters, one finds that there is now a *curve* (blue) of points in  $(a, b)$  space where stability is lost, where the stable solution will suddenly jump to an alternate outcome.

But in a cusp geometry the bifurcation curve loops back on itself, giving a second branch where this alternate solution itself loses stability, and will make a jump back to the original solution set. By repeatedly increasing  $b$  and then decreasing it, one can therefore observe hysteresis loops, as the system alternately follows one solution, jumps to the other, follows the other back, then jumps back to the first.

However, this is only possible in the region of parameter space  $a < 0$ . As  $a$  is increased, the hysteresis loops become smaller and smaller, until above  $a = 0$  they disappear altogether (the cusp catastrophe), and there is only one stable solution.

One can also consider what happens if one holds  $b$  constant and varies  $a$ . In the symmetrical case  $b = 0$ , one observes a pitchfork bifurcation as  $a$  is reduced, with one stable solution suddenly splitting into two stable solutions and one unstable solution as the physical system passes to  $a < 0$  through the cusp point (0,0) (an example of spontaneous symmetry breaking). Away from the cusp point, there is no sudden change in a physical solution being followed: when passing through the curve of fold bifurcations, all that happens is an alternate second solution becomes available.

A famous suggestion is that the cusp catastrophe can be used to model the behaviour of a stressed dog, which may respond by becoming cowed or becoming angry. The suggestion is that at moderate stress ( $a > 0$ ), the dog will exhibit a smooth transition of response from cowed to angry, depending on how it is provoked. But higher stress levels correspond to moving to the region ( $a < 0$ ). Then, if the dog starts cowed, it will remain cowed as it is irritated more and more, until it reaches the 'fold' point, when it will suddenly, discontinuously snap through to angry mode. Once in 'angry' mode, it will remain angry, even if the direct irritation parameter is considerably reduced.

Another application example is for the outer sphere electron transfer frequently encountered in chemical and biological systems (Xu, F. Application of catastrophe theory to the  $\Delta G^\ddagger$  to  $-\Delta G$  relationship in electron transfer reactions. *Zeitschrift für Physikalische Chemie Neue Folge* 166, 79-91 (1990)).

Fold bifurcations and the cusp geometry are by far the most important practical consequences of catastrophe theory. They are patterns which reoccur again and again in physics, engineering and mathematical modelling. They are the only way we currently have of detecting black holes and the dark matter of the universe, via the phenomenon of gravitational lensing producing multiple images of distant quasars.

The remaining simple catastrophe geometries are very specialised in comparison, and presented here only for curiosity value.

### Swallowtail catastrophe

$$V = x^5 + ax^3 + bx^2 + cx$$

The control parameter space is three dimensional. The bifurcation set in parameter space is made up of three surfaces of fold bifurcations, which meet in two lines of cusp bifurcations, which in turn meet at a single swallowtail bifurcation point.

As the parameters go through the surface of fold bifurcations, one minimum and one maximum of the potential function disappear. At the cusp bifurcations, two minima and one maximum are replaced by one minimum; beyond them the fold bifurcations disappear. At the swallowtail point, two minima and two maxima all meet at a single value of  $x$ . For values of  $a > 0$ , beyond the swallowtail, there is either one maximum-minimum pair, or none at all, depending on the values of  $b$  and  $c$ . Two of the surfaces of fold bifurcations, and the two lines of cusp bifurcations where they meet for  $a < 0$ , therefore disappear at the swallowtail point, to be replaced with only a single surface of fold bifurcations remaining. Salvador Dalí's last painting, *The Swallow's Tail*, was based on this catastrophe.

### Butterfly catastrophe

$$V = x^6 + ax^4 + bx^3 + cx^2 + dx$$

Depending on the parameter values, the potential function may have three, two, or one different local minima, separated by the loci of fold bifurcations. At the butterfly point, the different 3-surfaces of fold bifurcations, the 2-surfaces of cusp bifurcations, and the lines of swallowtail bifurcations all meet up and disappear, leaving a single cusp structure remaining when  $a > 0$

## Potential functions of two active variables

Umbilic catastrophes are examples of corank 2 catastrophes. They can be observed in optics in the focal surfaces created by light reflecting off a surface in three dimensions and are intimately connected with the geometry of nearly spherical surfaces. Thom proposed that the Hyperbolic umbilic catastrophe modeled the breaking of a wave and the elliptical umbilic modeled the creation of hair like structures.

### Hyperbolic umbilic catastrophe

$$V = x^3 + y^3 + axy + bx + cy$$

### Elliptic umbilic catastrophe

$$V = \frac{x^3}{3} - xy^2 + a(x^2 + y^2) + bx + cy$$

### Parabolic umbilic catastrophe

$$V = x^2y + y^4 + ax^2 + by^2 + cx + dy$$

## Arnold's notation

Vladimir Arnold gave the catastrophes the ADE classification, due to a deep connection with simple Lie groups.

- $A_0$  - a non-singular point:  $V = x$ .
- $A_1$  - a local extremum, either a stable minimum or unstable maximum  $V = \pm x^2 + ax$ .
- $A_2$  - the fold
- $A_3$  - the cusp
- $A_4$  - the swallowtail
- $A_5$  - the butterfly
- $A_k$  - a representative of an infinite sequence of one variable forms  $V = x^{k+1} + \dots$
- $D_4^-$  - the elliptical umbilic
- $D_4^+$  - the hyperbolic umbilic
- $D_5$  - the parabolic umbilic
- $D_k$  - a representative of an infinite sequence of further umbilic forms
- $E_6$  - the symbolic umbilic  $V = x^3 + y^4 + axy^2 + bxy + cx + dy + ey^2$
- $E_7$
- $E_8$

There are objects in singularity theory which correspond to most of the other simple Lie groups.

## See also

- broken symmetry
- tipping point
- phase transition
- domino effect
- snowball effect
- butterfly effect
- spontaneous symmetry breaking
- chaos theory

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## External links

- [CompLexicon: Catastrophe Theory](#) <sup>[1]</sup>
- [Catastrophe teacher](#) <sup>[2]</sup>

## References

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[2] [http://perso.wanadoo.fr/l.d.v.dujardin/ct/eng\\_index.html](http://perso.wanadoo.fr/l.d.v.dujardin/ct/eng_index.html)

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# Society for Mathematical Biology

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**The Society for Mathematical Biology (SMB)** is an international association cofounded in 1972 in USA by Drs. George Karreman, Herbert Daniel Landahl and (initially chaired) by Anthony Bartholomay for the furtherance of joint scientific activities between Mathematics and Biology research communities<sup>[1]</sup>. SMB publishes the "*Bulletin of Mathematical Biology*"<sup>[2]</sup> (ISSN 1522–9602)<sup>[3]</sup> <sup>[4]</sup>, as well as the SMB annual newsletter.

## History of The Society for Mathematical Biology

The Society for Mathematical Biology emerged and grew from the earlier school of mathematical biophysics, initiated and vigorously supported by the Founder of Mathematical Biology, Nicolas Rashevsky<sup>[5]</sup> <sup>[6]</sup>. Thus, the roots of SMB go back to the publication in 1939 of the first international journal of mathematical biology, previously entitled "The Bulletin of Mathematical Biophysics"<sup>[6]</sup>-- which was founded by Nicolas Rashevsky, and which is currently published by SMB under the name of "*Bulletin of Mathematical Biology*"<sup>[7]</sup>. Professor Rashevsky also founded in 1969 the non-profit organization "*Mathematical Biology, Incorporated*"--the precursor of SMB. Another notable member of the University of Chicago school of mathematical biology was Anatol Rapoport whose major interests were in developing basic concepts in the related area of mathematical sociology, who cofounded the Society for General Systems Research and became a president of the latter society in 1965. Herbert D. Landahl was initially also a member of Rashevsky's school of mathematical biology, and became the second president of SMB in the 1980s; both Herbert Landahl and Robert Rosen from Rashevsky's research group were focused on dynamical systems approaches to complex systems biology, with the latter researcher becoming in 1980 the president of the Society for General Systems Research.

## Research and educational activities

In addition to its research and news publications, The Society for Mathematical Biology supports education in: mathematical biology, mathematical biophysics, complex systems biology and theoretical biology through sponsorship of several topic-focused graduate and postdoctoral courses. To encourage and stimulate young researchers in this relatively new and rapidly developing field of mathematical biology *The Society for Mathematical Biology* awards several prizes, as well as lists regularly new open international opportunities for researchers and students in this field<sup>[8]</sup>.

## Further reading

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## See also

- George Karreman
  - Mathematical Biology
  - Quantum Biology
  - Quantum Biophysics
- Nicolas Rashevsky
  - Mathematical Biophysics
  - "*The Bulletin of Mathematical Biophysics*"<sup>[10]</sup>
  - Biocybernetics
  - Neuro cybernetics
  - Principles of Biology
  - Mathematical modeling of biosystems
  - Organismic set theory
  - Organism
  - Organization
  - Organismic sets of zeroth order
  - Epigenetic landscape
  - Two-factor theory of nerve impulse
  - Topology
  - Organismic development
  - Mathematical logic
  - Relation algebra
  - Mathematical sociology
- Anatol Rapoport
  - Systems science
  - Science education
  - Society for General Systems Research
  - Center for Advanced Study in the Behavioral Sciences
  - American Association for the Advancement of Science
  - International Society for the Systems Sciences
- Herbert Daniel Landahl
  - Biodynamics
  - Mathematical Biophysics of the Central nervous system
- Robert Rosen
  - Complex Systems Biology
  - Society for General Systems Research
  - Theoretical biology
  - Dynamical systems
  - Symbolic logic
  - Quantum Genetics
  - Bioinformatics
  - Graph theory



- Algebraic topology
- Category theory
- Network theory
- Control theory
- Ludwig von Bertalanffy
  - Society for General Systems Research
- Warren McCulloch-Neural networks
  - Neuro cybernetics
- Walter Pitts-Neural networks
  - Neural networks
  - Neuro cybernetics

## External links

- *The Society for Mathematical Biology* <sup>[13]</sup>
- Bulletin of Mathematical Biology <sup>[6]</sup>
- "In Memory of George Karreman." <sup>[11]</sup>—the first SMB President, by Paul De Weer.
- SMB home page <sup>[13]</sup>
- IFSR Home page <sup>[12]</sup> of "The International Federation for Systems Research" (IFSR)
- European Society for Mathematical and Theoretical Biology (ESMTB) <sup>[9]</sup>
- The Centre for Mathematical Biology (CMB) at the [[University of Oxford <sup>[13]</sup>]]

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- [3] "Bulletin of Mathematical Biology" (<http://www.springer.com/math/biology/journal/11538>) (in English). Springer New York. . Retrieved 2009-06-25.
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- [7] The Bulletin of Mathematical Biophysics (<http://www.springerlink.com/content/x513p402w52w1128/>)
- [8] <http://www.smb.org/prizes/index.shtml> SMB Mathematical Biology Prize Awards
- [9] <http://eprints.maths.ox.ac.uk/567/1/224.pdf>
- [10] <http://people.maths.ox.ac.uk/maini/PKM%20publications/170.pdf>
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- [12] <http://www.ifsr.org/>
- [13] <http://www2.maths.ox.ac.uk/cmb/>

# Organismic set theory

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*For the musical concepts, see Set theory (music).*

**Set theory** is the branch of mathematics that studies sets, which are collections of objects. Although any type of object can be collected into a set, set theory is applied most often to objects that are relevant to mathematics.

The modern study of set theory was initiated by Georg Cantor and Richard Dedekind in the 1870s. After the discovery of paradoxes in naive set theory, numerous axiom systems were proposed in the early twentieth century, of which the Zermelo–Fraenkel axioms, with the axiom of choice, are the best-known.

The language of set theory is used in the definitions of nearly all mathematical objects, such as functions, and concepts of set theory are integrated throughout the mathematics curriculum. Elementary facts about sets and set membership can be introduced in primary school, along with Venn and Euler diagrams, to study collections of commonplace physical objects. Elementary operations such as set union and intersection can be studied in this context. More advanced concepts such as cardinality are a standard part of the undergraduate mathematics curriculum.

Set theory is commonly employed as a foundational system for mathematics, particularly in the form of Zermelo–Fraenkel set theory with the axiom of choice. Beyond its foundational role, set theory is a branch of mathematics in its own right, with an active research community. Contemporary research into set theory includes a diverse collection of topics, ranging from the structure of the real number line to the study of the consistency of large cardinals.

## History

Mathematical topics typically emerge and evolve through interactions among many researchers. Set theory, however, was founded by a single paper in 1874 by Georg Cantor: "On a Characteristic Property of All Real Algebraic Numbers".<sup>[1] [2]</sup>

Beginning with the work of Zeno around 450 BC, mathematicians had been struggling with the concept of infinity. Especially notable is the work of Bernard Bolzano in the first half of the 19th century. The modern understanding of infinity began 1867-71, with Cantor's work on number theory. An 1872 meeting between Cantor and Richard Dedekind influenced Cantor's thinking and culminated in Cantor's 1874 paper.

Cantor's work initially polarized the mathematicians of his day. While Karl Weierstrass and Dedekind supported Cantor, Leopold Kronecker, now seen as a founder of mathematical constructivism, did not. Cantorian set theory eventually became widespread, due to the utility of Cantorian concepts, such as one-to-one correspondence among sets, his proof that there are more real numbers than integers, and the "infinity of infinities" ("Cantor's paradise") the power set operation gives rise to.

The next wave of excitement in set theory came around 1900, when it was discovered that Cantorian set theory gave rise to several contradictions, called antinomies or paradoxes. Bertrand Russell and Ernst Zermelo independently found the simplest and best known paradox, now called Russell's paradox and involving "the set of all sets that are not members of themselves." This leads to a contradiction, since it must be a member of itself and not a member of itself. In 1899 Cantor had himself posed the question: "what is the cardinal number of the set of all sets?" and obtained a related paradox.

The momentum of set theory was such that debate on the paradoxes did not lead to its abandonment. The work of Zermelo in 1908 and Abraham Fraenkel in 1922 resulted in the canonical axiomatic set theory ZFC, which is thought to be free of paradoxes. The work of analysts such as Henri Lebesgue demonstrated the great mathematical utility of set theory. Axiomatic set theory has become woven into the very fabric of mathematics as we know it today.

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## Basic concepts

Set theory begins with a fundamental binary relation between an object  $o$  and a set  $A$ . If  $o$  is a **member** (or **element**) of  $A$ , we write  $o \in A$ . Since sets are objects, the membership relation can relate sets as well.

A derived binary relation between two sets is the subset relation, also called **set inclusion**. If all the members of set  $A$  are also members of set  $B$ , then  $A$  is a **subset** of  $B$ , denoted  $A \subseteq B$ . For example,  $\{1,2\}$  is a subset of  $\{1,2,3\}$ , but  $\{1,4\}$  is not. From this definition, it is clear that a set is a subset of itself; in cases where one wishes to avoid this, the term **proper subset** is defined to exclude this possibility.

Just as arithmetic features binary operations on numbers, set theory features binary operations on sets. The:

- **Union** of the sets  $A$  and  $B$ , denoted  $A \cup B$ , is the set of all objects that are a member of  $A$ , or  $B$ , or both. The union of  $\{1, 2, 3\}$  and  $\{2, 3, 4\}$  is the set  $\{1, 2, 3, 4\}$ .
- **Intersection** of the sets  $A$  and  $B$ , denoted  $A \cap B$ , is the set of all objects that are members of both  $A$  and  $B$ . The intersection of  $\{1, 2, 3\}$  and  $\{2, 3, 4\}$  is the set  $\{2, 3\}$ .
- **Complement** of set  $A$  relative to set  $U$ , denoted  $A^c$ , is the set of all members of  $U$  that are not members of  $A$ . This terminology is most commonly employed when  $U$  is a universal set, as in the study of Venn diagrams. This operation is also called the **set difference** of  $U$  and  $A$ , denoted  $U \setminus A$ . The complement of  $\{1,2,3\}$  relative to  $\{2,3,4\}$  is  $\{4\}$ , while, conversely, the complement of  $\{2,3,4\}$  relative to  $\{1,2,3\}$  is  $\{1\}$ .
- **Symmetric difference** of sets  $A$  and  $B$  is the set of all objects that are a member of exactly one of  $A$  and  $B$  (elements which are in one of the sets, but not in both). For instance, for the sets  $\{1,2,3\}$  and  $\{2,3,4\}$ , the symmetric difference set is  $\{1,4\}$ . It is the set difference of the union and the intersection,  $(A \cup B) \setminus (A \cap B)$ .
- **Cartesian product** of  $A$  and  $B$ , denoted  $A \times B$ , is the set whose members are all possible ordered pairs  $(a,b)$  where  $a$  is a member of  $A$  and  $b$  is a member of  $B$ .
- **Power set** of a set  $A$  is the set whose members are all possible subsets of  $A$ . For example, the powerset of  $\{1, 2\}$  is  $\{\{\}, \{1\}, \{2\}, \{1,2\}\}$ .

## Some ontology

A set is pure if all of its members are sets, all members of its members are sets, and so on. For example, the set containing only the empty set is a nonempty pure set. When doing set theory, it is common to restrict attention to the pure sets, and many systems of axiomatic set theory are designed to axiomatize the pure sets only.

A key idea in set theory is the von Neumann universe of pure sets. Sets in this universe are arranged in a cumulative hierarchy, based on how deeply their members, members of members, etc. are nested. Each set is assigned an ordinal number  $\alpha$  in this hierarchy, known as its **rank**. A set is assigned a rank by transfinite recursion: if the least upper bound on the ranks of the members of a set  $X$  is  $\alpha$  then  $X$  is assigned rank  $\alpha+1$ . Also, for each ordinal  $\alpha$ , the set  $V_\alpha$  contains all sets assigned a rank less than  $\alpha$ .

## Axiomatic set theory

Elementary set theory can be studied informally and intuitively, and so can be taught in primary schools using, say, Venn diagrams. The intuitive approach silently assumes that all objects in the universe of discourse satisfying any defining condition form a set. This assumption gives rise to antinomies, the simplest and best known of which being Russell's paradox. Axiomatic set theory was originally devised to rid set theory of such antinomies<sup>[3]</sup>.

The most widely studied systems of axiomatic set theory imply that all sets form a cumulative hierarchy. Such systems come in two flavors, those whose ontology consists of:

- *Sets alone*. This includes the most common axiomatic set theory, Zermelo–Fraenkel set theory (ZFC), which includes the axiom of choice. Fragments of ZFC include:
  - Zermelo set theory, which replaces the axiom schema of replacement with that of separation;

- General set theory, a small fragment of Zermelo set theory sufficient for the Peano axioms and finite sets;
- Kripke-Platek set theory, which omits the axioms of infinity, powerset, and choice, and weakens the axiom schemata of separation and replacement.
- *Sets and proper classes*. This includes Von Neumann-Bernays-Gödel set theory, which has the same strength as ZFC for theorems about sets alone, and Morse-Kelley set theory, which is stronger than ZFC.

For the above systems, allowing urelements (objects that can be members of sets while having no members themselves) does not give rise to any interesting mathematics.

The systems NFU (allowing urelements) and NF (lacking them), though having their origin in type theory, are not based on a cumulative hierarchy. NF and NFU include a "set of everything," relative to which every set has a complement. Here urelements matter, because NF, but not NFU, produces sets for which the axiom of choice does not hold.

Systems of constructive set theory, such as CST, CZF, and IZF, embed their set axioms in intuitionistic logic instead of first order logic. Yet other systems accept standard first order logic but feature a nonstandard membership relation. These include rough set theory and fuzzy set theory, in which the value of an atomic formula embodying the membership relation is not simply **True** and **False**. The Boolean-valued models of ZFC are a related subject.

## Applications

Nearly all mathematical concepts are now defined formally in terms of sets and set theoretic concepts. For example, mathematical structures as diverse as graphs, manifolds, rings, and vector spaces are all defined as sets having various (axiomatic) properties. Equivalence and order relations are ubiquitous in mathematics, and the theory of relations is entirely grounded in set theory.

Set theory is also a promising foundational system for much of mathematics. Since the publication of the first volume of *Principia Mathematica*, it has been claimed that most or even all mathematical theorems can be derived using an aptly designed set of axioms for set theory, augmented with many definitions, using first or second order logic. For example, properties of the natural and real numbers can be derived within set theory, as each number system can be identified with a set of equivalence classes under a suitable equivalence relation whose field is some infinite set.

Set theory as a foundation for mathematical analysis, topology, abstract algebra, and discrete mathematics is likewise uncontroversial; mathematicians accept that (in principle) theorems in these areas can be derived from the relevant definitions and the axioms of set theory. Few full derivations of complex mathematical theorems from set theory have been formally verified, however, because such formal derivations are often much longer than the natural language proofs mathematicians commonly present. One verification project, Metamath, includes derivations of more than 10,000 theorems starting from the ZFC axioms and using first order logic.

## Areas of study

Set theory is a major area of research in mathematics, with many interrelated subfields.

### Combinatorial set theory

**Combinatorial set theory** concerns extensions of finite combinatorics to infinite sets. This includes the study of cardinal arithmetic and the study of extensions of Ramsey's theorem such as the Erdos-Rado theorem.

### Descriptive set theory

**Descriptive set theory** is the study of subsets of the real line and, more generally, subsets of Polish spaces. It begins with the study of pointclasses in the Borel hierarchy and extends to the study of more complex hierarchies such as the projective hierarchy and the Wadge hierarchy. Many properties of Borel sets can be established in ZFC, but

proving these properties hold for more complicated sets requires additional axioms related to determinacy and large cardinals.

The field of effective descriptive set theory is between set theory and recursion theory. It includes the study of lightface pointclasses, and is closely related to hyperarithmetical theory. In many cases, results of classical descriptive set theory have effective versions; in some cases, new results are obtained by proving the effective version first and then extending ("relativizing") it to make it more broadly applicable.

A recent area of research concerns Borel equivalence relations and more complicated definable equivalence relations. This has important applications to the study of invariants in many fields of mathematics.

## Fuzzy set theory

In set theory as Cantor defined and Zermelo and Fraenkel axiomatized, an object is either a member of a set or not. In fuzzy set theory this condition was relaxed by Zadeh so an object has a *degree of membership* in a set, as number between 0 and 1. For example, the degree of membership of a person in the set of "tall people" is more flexible than a simple yes or no answer and can be a real number such as 0.75.

## Inner model theory

An **inner model** of Zermelo–Fraenkel set theory (ZF) is a transitive class that includes all the ordinals and satisfies all the axioms of ZF. The canonical example is the constructible universe  $L$  developed by Gödel. The study of inner models of extensions of ZF is of interest in set theory because it can be used to prove consistency results. For example, it can be shown that regardless whether a model  $V$  of ZF satisfies the continuum hypothesis or the axiom of choice, the inner model  $L$  constructed inside the original model will satisfy both the generalized continuum hypothesis and the axiom of choice. Thus the assumption that ZF is consistent (has any model whatsoever) implies that ZF together with these two principles is consistent.

The study of inner models is common in the study of determinacy and large cardinals, especially when considering axioms such as the axiom of determinacy that contradict the axiom of choice. Even if a fixed model of set theory satisfies the axiom of choice, it is possible for an inner model to fail to satisfy the axiom of choice. For example, the existence of sufficiently large cardinals implies that there is an inner model satisfying the axiom of determinacy (and thus not satisfying the axiom of choice).<sup>[4]</sup>

## Large cardinals

A **large cardinal** is a cardinal number with an extra property. Many such properties are studied, including inaccessible cardinals, measurable cardinals, and many more. These properties typically imply the cardinal number must be very large, with the existence of a cardinal with the specified property unprovable in Zermelo–Fraenkel set theory.

## Determinacy

**Determinacy** refers to the fact that, under appropriate assumptions, certain two-player games of perfect information are determined from the start in the sense that one player must have a winning strategy. The existence of these strategies has important consequences in descriptive set theory, as the assumption that a broader class of games is determined often implies that a broader class of sets will have a topological property. The axiom of determinacy (AD) is an important object of study; although incompatible with the axiom of choice, AD implies that all subsets of the real line are well behaved (in particular, measurable and with the perfect set property). AD can be used to prove that the Wadge degrees have an elegant structure.

## Forcing

Paul Cohen invented the method of forcing while searching for a model of ZFC in which the axiom of choice or the continuum hypothesis fails. Forcing adjoins to some given model of set theory additional sets in order to create a larger model with properties determined (i.e. "forced") by the construction and the original model. For example, Cohen's construction adjoins additional subsets of the natural numbers without changing any of the cardinal numbers of the original model. Forcing is also one of two methods for proving relative consistency by finitistic methods, the other method being Boolean-valued models.

## Cardinal invariants

A **cardinal invariant** is a property of the real line measured by a cardinal number. For example, a well-studied invariant is the smallest cardinality of a collection of meagre sets of reals whose union is the entire real line. These are invariants in the sense that any two isomorphic models of set theory must give the same cardinal for each invariant. Many cardinal invariants have been studied, and the relationships between them are often complex and related to axioms of set theory.

## Set-theoretic topology

**Set-theoretic topology** studies questions of general topology that are set-theoretic in nature or that require advanced methods of set theory for their solution. Many of these theorems are independent of ZFC, requiring stronger axioms for their proof. A famous problem is the normal Moore space question, a question in general topology that was the subject of intense research. The answer to the normal Moore space question was eventually proved to be independent of ZFC.

## Objections to set theory as a foundation for mathematics

From set theory's inception, some mathematicians objected to it as a foundation for mathematics, arguing, for example, that it is just a game which includes elements of fantasy. The most common objection to set theory, one Kronecker voiced in set theory's earliest years, starts from the constructivist view that mathematics is loosely related to computation. If this view is granted, then the treatment of infinite sets, both in naive and in axiomatic set theory, introduces into mathematics methods and objects that are not computable even in principle. Ludwig Wittgenstein questioned the way Zermelo–Fraenkel set theory handled infinities. Wittgenstein's views about the foundations of mathematics were later criticised by Paul Bernays, and closely investigated by Crispin Wright, among others.

Category theorists have proposed topos theory as an alternative to traditional axiomatic set theory. Topos theory can interpret various alternatives to that theory, such as constructivism, finite set theory, and computable set theory.

## See also

- Category theory
- List of set theory topics
- Musical set theory concerns the application of combinatorics and group theory to music; beyond the fact that it uses finite sets it has nothing to do with mathematical set theory of any kind. In the last two decades, transformational theory in music has taken the concepts of mathematical set theory more rigorously (see Lewin 1987).
- Relational model - Borrows from Set Theory.

## Further reading

- Keith Devlin, (2nd ed.) 1993. *The Joy of Sets*. Springer Verlag, ISBN 0-387-94094-4
- Tiles, Mary, 2004 (1989). *The Philosophy of Set Theory: An Historical Introduction to Cantor's Paradise*. Dover Publications.
- Johnson, Philip, 1972. *A History of Set Theory*. Prindle, Weber & Schmidt ISBN 0871501546
- Kunen, Kenneth, Set Theory: An Introduction to Independence Proofs. *North-Holland, 1980. ISBN 0-444-85401-0*.

## External links

- Foreman, M., Akihiro Kanamori, eds. *Handbook of Set Theory*. <sup>[5]</sup> 3 vols., 2010. Each chapter surveys some aspect of contemporary research in set theory. Does not cover established elementary set theory, on which see Devlin (1993).

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- [2] Philip Johnson, 1972, *A History of Set Theory*, Prindle, Weber & Schmidt ISBN 0871501546
- [3] In his 1925, John von Neumann observed that "set theory in its first, "naive" version, due to Cantor, led to contradictions. These are the well-known antinomies of the set of all sets that do not contain themselves (Russell), of the set of all transfinite ordinal numbers (Burali-Forti), and the set of all finitely definable real numbers (Richard)." He goes on to observe that two "tendencies" were attempting to "rehabilitate" set theory. Of the first effort, exemplified by Bertrand Russell, Julius König, Hermann Weyl and L. E. J. Brouwer, von Neumann called the "overall effect of their activity . . . devastating". With regards to the axiomatic method employed by second group composed of Zermelo, Abraham Fraenkel and Arthur Moritz Schoenflies, von Neumann worried that "We see only that the known modes of inference leading to the antinomies fail, but who knows where there are not others?" and he set to the task, "in the spirit of the second group", to "produce, by means of a finite number of purely formal operations . . . all the sets that we want to see formed" but not allow for the antinomies. (All quotes from von Neumann 1925 reprinted in van Heijenoort, Jean (1967, third printing 1976), "From Frege to Gödel: A Source Book in Mathematical Logic, 1979-1931", Harvard University Press, Cambridge MA, ISBN 0-674-32449-8 (pbk). A synopsis of the history, written by van Heijenoort, can be found in the comments that precede von Neumann's 1925.
- [4] Jech, Thomas (2003), *Set Theory: Third Millennium Edition*, Springer Monographs in Mathematics, Berlin, New York: Springer-Verlag, ISBN 978-3-540-44085-7, p. 642.
- [5] <http://www.tau.ac.il/~rinot/host.html>

# Organism

| Life on Earth                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                     |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|
| Fossil range: Archaeon - Recent                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                     |
|                                                                                                                                                                                                                                                                                                                                                                                                            |                                     |
| These <i>Escherichia coli</i> cells provide an example of a prokaryotic microorganism                                                                                                                                                                                                                                                                                                                                                                                                       |                                     |
| Scientific classification                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                     |
| (unranked):                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Life on Earth ( <i>Gaeabionta</i> ) |
| Domains and Kingdoms                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                     |
| <ul style="list-style-type: none"><li>Cellular life<ul style="list-style-type: none"><li>Bacteria</li><li>Archaea</li><li>Eukarya<ul style="list-style-type: none"><li>Bikonta<ul style="list-style-type: none"><li>Rhizaria</li><li>Excavata</li><li>Heterokonta</li><li>Alveolata</li><li>Plantae</li></ul></li><li>Unikonta<ul style="list-style-type: none"><li>Amoebozoa</li><li>Fungi</li><li>Animalia</li></ul></li></ul></li></ul></li><li>Non-cellular life (viruses) **</li></ul> |                                     |

In biology, an **organism** is any living system (such as animal, plant, fungus, or micro-organism). In at least some form, all organisms are capable of response to stimuli, reproduction, growth and development, and maintenance of homeostasis as a stable whole. An organism may either be unicellular (single-celled) or be composed of, as in humans, many billions of cells grouped into specialized tissues and organs. The term *multicellular* (many-celled) describes any organism made up of more than one cell.

The term "organism" (Greek *ὁργανισμός* - *organismos*, from Ancient Greek *ὄργανον* - *organon* "organ, instrument, tool") first appeared in the English language in 1701 and took on its current definition by 1834 (Oxford English Dictionary).

Scientific classification in biology considers organisms synonymous with **life on Earth**. Based on cell type, organisms may be divided into the prokaryotic and eukaryotic groups. The prokaryotes represent two separate domains, the Bacteria and Archaea. Eukaryotic organisms,



A polypore mushroom has parasitic relationship with its host



with a membrane-bounded cell nucleus, also contain organelles, namely mitochondria and (in plants) plastids, generally considered to be derived from endosymbiotic bacteria.<sup>[1]</sup> Fungi, animals and plants are examples of species that are eukaryotes.

More recently a clade, Neomura, has been proposed, which groups together the Archaea and Eukarya. Neomura is thought to have evolved from Bacteria, more specifically from Actinobacteria.<sup>[2]</sup>

## Semantics

The word "*organism*" may broadly be defined as *an assembly of molecules that function as a more or less stable whole and has the properties of life*. However, many sources propose definitions that exclude viruses and theoretically-possible man-made non-organic life forms.<sup>[3]</sup> Viruses are dependent on the biochemical machinery of a host cell for reproduction.

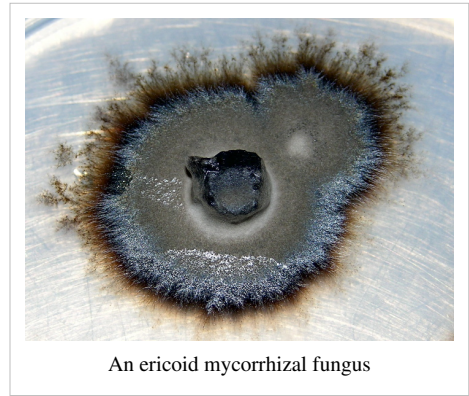
Chambers Online Reference provides a broad definition: "any living structure, such as a plant, animal, fungus or bacterium, capable of growth and reproduction".<sup>[4]</sup>

In multicellular life the word "organism" usually describes the whole hierarchical assemblage of systems (for example circulatory, digestive, or reproductive) themselves collections of organs; these are, in turn, collections of tissues, which are themselves made of cells. In some plants and the nematode *Caenorhabditis elegans*, individual cells are totipotent.

A superorganism is an organism consisting of many individuals working together as a single functional or social unit.

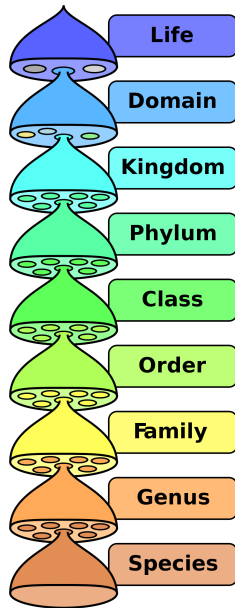
## Viruses

Viruses are not typically considered to be organisms because they are incapable of "independent" or autonomous reproduction or metabolism. This controversy is problematic because some cellular organisms also incapable of independent survival (but not of independent metabolism and procreation) and live as obligatory intracellular parasites. Although viruses have a few enzymes and molecules characteristic of living organisms, they have no metabolism of their own and cannot synthesize and organize the organic compounds that form them. Naturally, this rules out autonomous reproduction and they can only be passively replicated by the machinery of the host cell. In this sense they are similar to inanimate matter. While viruses sustain no independent metabolism, and thus are usually not accounted organisms, they do have their own genes and they do evolve by similar mechanisms by which organisms evolve.



An ericoid mycorrhizal fungus

## Organizational terminology



The hierarchy of biological classification's eight major taxonomic ranks. Intermediate minor rankings are not shown.



All organisms are classified by the science of alpha taxonomy into either taxa or clades.

Taxa are ranked groups of organisms, which run from the general (domain) to the specific (species). A broad scheme of ranks in hierarchical order is:

- Domain
- Kingdom
- Phylum
- Class
- Order
- Family
- Genus
- Species

To give an example, *Homo sapiens* is the Latin binomial equating to modern humans. All members of the species *sapiens* are, at least in theory, genetically able to interbreed. Several species may belong to a genus, but the members of different species within a genus are unable to interbreed to produce fertile offspring. *Homo*, however, only has one surviving species (*sapiens*); *Homo erectus*, *Homo neanderthalensis*, &c. having become extinct thousands of years ago. Several genera belong to the same family and so on up the hierarchy. Eventually, the relevant kingdom (Animalia, in the case of humans) is placed into one of the three domains depending upon certain genetic and structural characteristics.

All living organisms known to science are given classification by this system such that the species within a particular family are more closely related and genetically similar than the species within a particular phylum.

## Chemistry

Organisms are complex chemical systems, organized in ways that promote reproduction and some measure of sustainability or survival. The molecular phenomena of chemistry are fundamental in understanding organisms, but it is a philosophical error (reductionism) to reduce organismal biology to mere chemistry. It is generally the phenomena of entire organisms that determine their fitness to an environment and therefore the survivability of their DNA based genes.

Organisms clearly owe their origin, metabolism, and many other internal functions to chemical phenomena, especially the chemistry of large organic molecules. Organisms are complex systems of chemical compounds which, through interaction with each other and the environment, play a wide variety of roles.

Organisms are semi-closed chemical systems. Although they are individual units of life (as the definition requires) they are not closed to the environment around them. To operate they constantly take in and release energy. Autotrophs produce usable energy (in the form of organic compounds) using light from the sun or inorganic compounds while heterotrophs take in organic compounds from the environment.

The primary chemical element in these compounds is carbon. The physical properties of this element such as its great affinity for bonding with other small atoms, including other carbon atoms, and its small size makes it capable of forming multiple bonds, make it ideal as the basis of organic life. It is able to form small three-atom compounds (such as carbon dioxide), as well as large chains of many thousands of atoms that can store data (nucleic acids), hold cells together, and transmit information (protein).



A crab is an example of an organism.

## Macromolecules

Compounds that make up organisms may be divided into macromolecules and other, smaller molecules. The four groups of macromolecule are nucleic acids, proteins, carbohydrates and lipids. Nucleic acids (specifically deoxyribonucleic acid, or DNA) store genetic data as a sequence of nucleotides. The particular sequence of the four different types of nucleotides (adenine, cytosine, guanine, and thymine) dictate the many characteristics that constitute the organism. The sequence is divided up into codons, each of which is a particular sequence of three nucleotides and corresponds to a particular amino acid. Thus a sequence of DNA codes for a particular protein which, due to the chemical properties of the amino acids of which it is made, folds in a particular manner and so performs a particular function.

The following functions of protein have been recognized:

1. Enzymes, which catalyze all of the reactions of metabolism;
2. Structural proteins, such as tubulin, or collagen;
3. Regulatory proteins, such as transcription factors or cyclins that regulate the cell cycle;
4. Signaling molecules or their receptors such as some hormones and their receptors;
5. Defensive proteins, which can include everything from antibodies of the immune system, to toxins (e.g., dendrotoxins of snakes), to proteins that include unusual amino acids like canavanine.

Lipids make up the membrane of cells that constitutes a barrier, containing everything within the cell and preventing compounds from freely passing into, and out of, the cell. In some multicellular organisms they serve to store energy and mediate communication between cells. Carbohydrates also store and transport energy in some organisms, but are more easily broken down than lipids.

## Structure

All organisms consist of monomeric units called cells; some contain a single cell (unicellular) and others contain many units (multicellular). Multicellular organisms are able to specialize cells to perform specific functions, a group of such cells is tissue the four basic types of which are epithelium, nervous tissue, muscle tissue and connective tissue. Several types of tissue work together in the form of an organ to produce a particular function (such as the pumping of the blood by the heart, or as a barrier to the environment as the skin). This pattern continues to a higher level with several organs functioning as an organ system to allow for reproduction, digestion, &c. Many multicelled organisms consist of several organ systems, which coordinate to allow for life.

## The cell

The cell theory, first developed in 1839 by Schleiden and Schwann, states that all organisms are composed of one or more cells; all cells come from preexisting cells; all vital functions of an organism occur within cells, and cells contain the hereditary information necessary for regulating cell functions and for transmitting information to the next generation of cells.

There are two types of cells, eukaryotic and prokaryotic. Prokaryotic cells are usually singletons, while eukaryotic cells are usually found in multi-cellular organisms. Prokaryotic cells lack a nuclear membrane so DNA is unbound within the cell, eukaryotic cells have nuclear membranes.

All cells, whether prokaryotic or eukaryotic, have a membrane, which envelops the cell, separates its interior from its environment, regulates what moves in and out, and maintains the electric potential of the cell. Inside the membrane, a salty cytoplasm takes up most of the cell volume. All cells possess DNA, the hereditary material of genes, and RNA, containing the information necessary to build various proteins such as enzymes, the cell's primary machinery. There are also other kinds of biomolecules in cells.

All cells share several abilities:<sup>[5]</sup>

- Reproduction by cell division (binary fission, mitosis or meiosis).
- Use of enzymes and other proteins coded for by DNA genes and made via messenger RNA intermediates and ribosomes.
- Metabolism, including taking in raw materials, building cell components, converting energy, molecules and releasing by-products. The functioning of a cell depends upon its ability to extract and use chemical energy stored in organic molecules. This energy is derived from metabolic pathways.
- Response to external and internal stimuli such as changes in temperature, pH or nutrient levels.
- Cell contents are contained within a cell surface membrane that contains proteins and a lipid bilayer.

## Life span

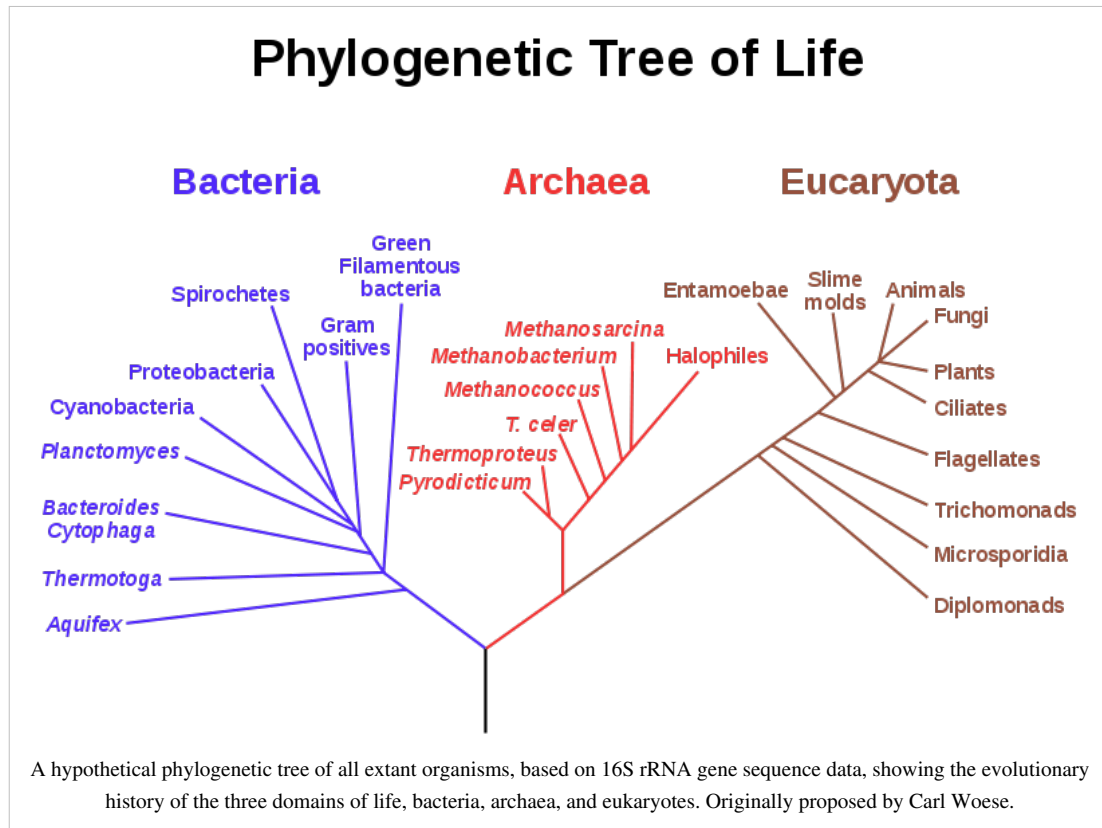
One of the basic parameters of organism is its life span. Some organisms live as short as one day, while some plants can live thousands of years. Aging is important when determining life span of most organisms, bacterium, a virus or even a prion.

## Evolution

In biology, the theory of universal common descent proposes that all organisms on Earth are descended from a common ancestor or ancestral gene pool. Evidence for common descent may be found in traits shared between all living organisms. In Darwin's day, the evidence of shared traits was based solely on visible observation of morphologic similarities, such as the fact that all birds have wings, even those that do not fly.

Today, there is debate over whether or not all organisms descended from a common ancestor, or a "last universal ancestor" (LUA), also called the "last universal common ancestor" (LUCA). The universality of genetic coding

suggests common ancestry. For example, every living cell makes use of nucleic acids as its genetic material, and uses the same twenty amino acids as the building blocks for proteins, although exceptions to the basic twenty amino acids have been found. However, throughout history groupings based on appearance or function of species have sometimes been polyphyletic due to convergent evolution.



The "last universal ancestor" (LUA), or "last universal common ancestor" (LUCA), is the name given to the hypothetical single cellular organism or single cell that gave rise to all life on Earth 3.5 to 3.8 billion years ago<sup>[6]</sup>; however, this hypothesis has since been refuted on many grounds. For example, it was once thought that the genetic code was universal (see: universal genetic code), but many variations have been discovered<sup>[7]</sup> including various alternative mitochondrial codes.<sup>[8]</sup> Back in the early 1970s, evolutionary biologists thought that a given piece of DNA specified the same protein subunit in every living thing, and that the genetic code was thus universal. This was interpreted as evidence that every organism had inherited its genetic code from a single common ancestor, aka, an LUCA. In 1979, however, exceptions to the code were found in mitochondria, the tiny energy factories inside cells. Researchers studying human mitochondrial genes discovered that they used an alternative code, and many slight variants have been discovered since,<sup>[9]</sup> including various alternative mitochondrial codes,<sup>[10]</sup> as well as small variants such as *Mycoplasma* translating the codon UGA as tryptophan. Biologists subsequently found exceptions in bacteria and in the nuclei of algae and single-celled animals. For example, certain proteins may use alternative initiation (start) codons not normally used by that species.<sup>[11]</sup> In certain proteins, non-standard amino acids are substituted for standard stop codons, depending upon associated signal sequences in the messenger RNA: UGA can code for selenocysteine and UAG can code for pyrrolysine. Selenocysteine is now viewed as the 21st amino acid, and pyrrolysine is viewed as the 22nd. A detailed description of variations in the genetic code can be found at the NCBI web site<sup>[12]</sup>.

It is now clear that the genetic code is not the same in all living things and this provides credence that all living things did not evolve on a firmly-rooted tree of life from a single LUCA. Further support that there is no LUCA has been provided over the years by horizontal/lateral gene transfer in both prokaryote and eukaryote single cell organisms. This is why phylogenetic trees cannot be rooted; why almost all phylogenetic trees have different



branching structures, particularly near the base of the tree; and why many organisms have been found with codons and sections of their DNA sequence that are sometimes unrelated to other species.<sup>[13]</sup>

Information about the early development of life includes input from many different fields, including geology and planetary science. These sciences provide information about the history of the Earth and the changes produced by life. However, a great deal of information about the early Earth has been destroyed by geological processes over the course of time.

## History of life

The chemical evolution from self-catalytic chemical reactions to life (see Origin of life) is not a part of biological evolution, but it is unclear at which point such increasingly complex sets of reactions became what we would consider, today, to be living organisms.

Not much is known about the earliest developments in life. However, all existing organisms share certain traits, including cellular structure and genetic code. Most scientists interpret this to mean all existing organisms share a common ancestor, which had already developed the most fundamental cellular processes, but there is no scientific consensus on the relationship of the three domains of life (Archaea, Bacteria, Eukaryota) or the origin of life. Attempts to shed light on the earliest history of life generally focus on the behavior of macromolecules, particularly RNA, and the behavior of complex systems.

The emergence of oxygenic photosynthesis (around 3 billion years ago) and the subsequent emergence of an oxygen-rich, non-reducing atmosphere can be traced through the formation of banded iron deposits, and later red beds of iron oxides. This was a necessary prerequisite for the development of aerobic cellular respiration, believed to have emerged around 2 billion years ago.

In the last billion years, simple multicellular plants and animals began to appear in the oceans. Soon after the emergence of the first animals, the Cambrian explosion (a period of unrivaled and remarkable, but brief, organismal diversity documented in the fossils found at the Burgess Shale) saw the creation of all the major body plans, or phyla, of modern animals. This event is now believed to have been triggered by the development of the Hox genes. About 500 million years ago, plants and fungi colonized the land, and were soon followed by arthropods and other animals, leading to the development of today's land ecosystems.

The evolutionary process may be exceedingly slow. Fossil evidence indicates that the diversity and complexity of modern life has developed over much of the history of the earth. Geological evidence indicates that the Earth is approximately 4.6 billion years old. Studies on guppies by David Reznick at the University of California, Riverside, however, have shown that the rate of evolution through natural selection can proceed 10 thousand to 10 million times faster than what is indicated in the fossil record.<sup>[14]</sup> Such comparative studies however are invariably biased by disparities in the time scales over which evolutionary change is measured in the laboratory, field experiments, and the fossil record.



Precambrian stromatolites in the Siyeh Formation, Glacier National Park. In 2002, William Schopf of UCLA published a controversial paper in the journal *Nature* arguing that formations such as this possess 3.5 billion year old fossilized algae microbes. If true, they would be the earliest known life on earth.

## Horizontal gene transfer, and the history of life

The ancestry of living organisms has traditionally been reconstructed from morphology, but is increasingly supplemented with phylogenetics - the reconstruction of phylogenies by the comparison of genetic (DNA) sequence.

"Sequence comparisons suggest recent horizontal transfer of many genes among diverse species including across the boundaries of phylogenetic 'domains'. Thus determining the phylogenetic history of a species can not be done conclusively by determining evolutionary trees for single genes."<sup>[15]</sup>

Biologist Gogarten suggests "the original metaphor of a tree no longer fits the data from recent genome research", therefore "biologists [should] use the metaphor of a mosaic to describe the different histories combined in individual genomes and use [the] metaphor of a net to visualize the rich exchange and cooperative effects of HGT among microbes."<sup>[16]</sup>

## Future of life (cloning and synthetic organisms)

In modern terms, the category of organism cloning refers to the procedure of creating a new multicellular organism, genetically identical to another. However, cloning also has the potential of creating entirely new species of organisms. Organism cloning is the subject of much ethical debate (see Bioethics, Ethics of cloning, and Designer baby articles).

The J. Craig Venter Institute has recently assembled a synthetic yeast genome, *Mycoplasma genitalium*, by recombination of 25 overlapping DNA fragments in a single step. "The use of yeast recombination greatly simplifies the assembly of large DNA molecules from both synthetic and natural fragments."<sup>[17]</sup> Other companies, such as Synthetic Genomics, have already been formed to take advantage of the many commercial uses of custom designed genomes.

## External links

- BBCNews: 27 September, 2000, When slime is not so thick <sup>[18]</sup> Citat: "It means that some of the lowliest creatures in the plant and animal kingdoms, such as slime and amoeba, may not be as primitive as once thought"
- SpaceRef.com, July 29, 1997: Scientists Discover Methane Ice Worms On Gulf Of Mexico Sea Floor <sup>[19]</sup>
  - The Eberly College of Science: Methane Ice Worms discovered on Gulf of Mexico Sea Floor <sup>[20]</sup> download Publication quality photos
- Artikel, 2000: Methane Ice Worms: Hesiocaeca methanicola. Colonizing Fossil Fuel Reserves <sup>[21]</sup>
- SpaceRef.com, May 04, 2001: Redefining "Life as We Know it" <sup>[22]</sup> *Hesiocaeca methanicola* In 1997, Charles Fisher, professor of biology at Penn State, discovered this remarkable creature living on mounds of methane ice under half a mile of ocean on the floor of the Gulf of Mexico.
- BBCNews, 18 December, 2002, 'Space bugs' grown in lab <sup>[23]</sup> Citat: "*Bacillus simplex* and *Staphylococcus pasteurii*...*Engyodontium album* The strains cultured by Dr Wainwright seemed to be resistant to the effects of UV - one quality required for survival in space"
- BBCNews, 19 June, 2003, Ancient organism challenges cell evolution <sup>[24]</sup> Citat: "It appears that this organelle has been conserved in evolution from prokaryotes to eukaryotes, since it is present in both"
- Interactive Syllabus for General Biology - BI 04, Saint Anselm College, Summer 2003 <sup>[25]</sup>
- Jacob Feldman: Stramenopila <sup>[26]</sup>
- NCBI Taxonomy entry: root <sup>[27]</sup> (rich)
- Saint Anselm College: Survey of representatives of the major Kingdoms <sup>[28]</sup> Citat: "Number of kingdoms has not been resolved...Bacteria present a problem with their diversity...Protista present a problem with their diversity...",
- Species 2000 Indexing the world's known species <sup>[29]</sup>. Species 2000 has the objective of enumerating all known species of plants, animals, fungi and microbes on Earth as the baseline dataset for studies of global biodiversity. It will also provide a simple access point enabling users to link from here to other data systems for all groups of

organisms, using direct species-links.

- The largest organism in the world may be a fungus carpeting nearly 10 square kilometers of an Oregon forest, and may be as old as 10500 years. <sup>[30]</sup>
- The Tree of Life <sup>[31]</sup>.
- Frequent questions from kids about life and their answers <sup>[32]</sup>

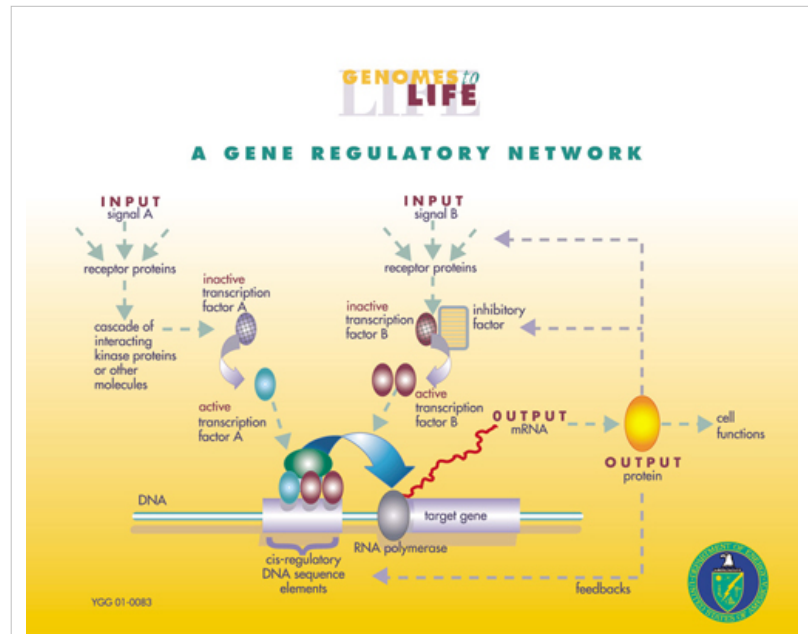
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- [2] T. Cavalier-Smith (2002) The neomuran origin of archaeobacteria, the negibacterial root of the universal tree and bacterial megaclassification. *International Journal of Systematic and Evolutionary Microbiology* 52, 7–76
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- [4] "organism". *Chambers 21st Century Dictionary* (online ed.). 1999.
- [5] The Universal Features of Cells on Earth ([http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Search&db=books&doptcmdl=GenBookHL&term="all+cells"+AND+mboc4\[book\]+AND+372023\[uid\]&rid=mboc4.section.4#23](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Search&db=books&doptcmdl=GenBookHL&term=)) in Chapter 1 of *Molecular Biology of the Cell* ([http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Search&db=books&doptcmdl=GenBookHL&term=cell+biology+AND+mboc4\[book\]+AND+373693\[uid\]&rid=mboc4](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Search&db=books&doptcmdl=GenBookHL&term=cell+biology+AND+mboc4[book]+AND+373693[uid]&rid=mboc4)) fourth edition, edited by Bruce Alberts (2002) published by Garland Science.
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- [15] Oklahoma State - Horizontal Gene Transfer (<http://opbs.okstate.edu/~melcher/MG/MGW3/MG334.html>)
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- [26] <http://www.personal.psu.edu/users/j/s/jsf165/Bio110.html>
- [27] <http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Root>
- [28] <http://www.anselm.edu/homepage/jpitocch/genbios/surveybi04.html>
- [29] <http://www.species2000.org/>
- [30] [http://www.abc.net.au/science/news/enviro/EnviroRepublish\\_828525.htm](http://www.abc.net.au/science/news/enviro/EnviroRepublish_828525.htm)
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- [32] <http://www.scribd.com/doc/1016/Life-from-birth-to-death/>

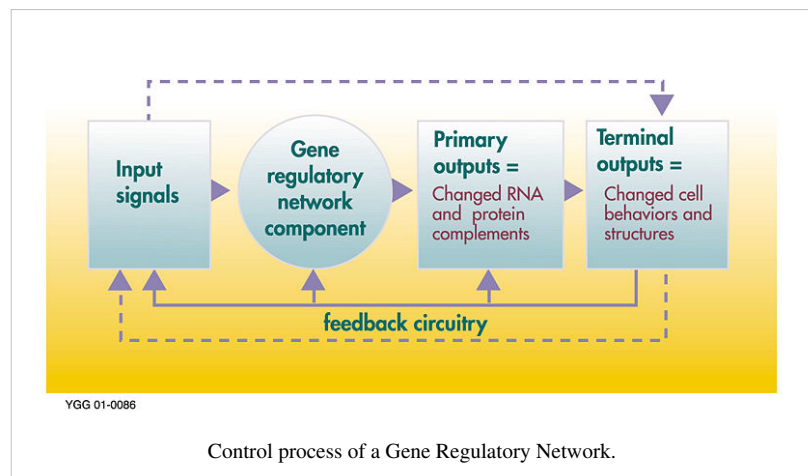


# Organismic sets of zeroth order

A **gene regulatory network** or **genetic regulatory network (GRN)** is a collection of DNA segments in a cell which interact with each other (indirectly through their RNA and protein expression products) and with other substances in the cell, thereby governing the rates at which genes in the network are transcribed into mRNA. In general, each mRNA molecule goes on to make a specific protein (or set of proteins). In some cases this protein will be structural, and will accumulate at the cell-wall or within the cell to give it particular structural properties. In other cases the protein will be an enzyme; a micro-machine that catalyses a certain reaction, such as the breakdown of a food source or toxin. Some proteins though serve only to activate other genes, and these are the transcription factors that are the main players in regulatory networks or cascades. By binding to the promoter region at the start of other genes they turn them on, initiating the production of another protein, and so on. Some transcription factors are inhibitory.



Structure of a Gene Regulatory Network.



Control process of a Gene Regulatory Network.

In single-celled organisms regulatory networks respond to the external environment, optimising the cell at a given time for survival in this environment. Thus a yeast cell, finding itself in a sugar solution, will turn on genes to make enzymes that process the sugar to alcohol.<sup>[1]</sup> This process, which we associate with wine-making, is how the yeast cell makes its living, gaining energy to multiply, which under normal circumstances would enhance its survival prospects.

In multicellular animals the same principle has been put in the service of gene cascades that control body-shape.<sup>[2]</sup> Each time a cell divides, two cells result which, although they contain the same genome in full, can differ in which genes are turned on and making proteins. Sometimes a 'self-sustaining feedback loop' ensures that a cell maintains its identity and passes it on. Less understood is the mechanism of epigenetics by which chromatin modification may provide cellular memory by blocking or allowing transcription. A major feature of multicellular animals is the use of morphogen gradients, which in effect provide a positioning system that tells a cell where in the body it is, and hence what sort of cell to become. A gene that is turned on in one cell may make a product that leaves the cell and diffuses through adjacent cells, entering them and turning on genes only when it is present above a certain threshold level. These cells are thus induced into a new fate, and may even generate other morphogens that signal back to the

original cell. Over longer distances morphogens may use the active process of signal transduction. Such signalling controls embryogenesis, the building of a body plan from scratch through a series of sequential steps. They also control maintain adult bodies through feedback processes, and the loss of such feedback because of a mutation can be responsible for the cell proliferation that is seen in cancer. In parallel with this process of building structure, the gene cascade turns on genes that make structural proteins that give each cell the physical properties it needs.

## Overview

At one level, biological cells can be thought of as "partially-mixed bags" of biological chemicals – in the discussion of gene regulatory networks, these chemicals are mostly the mRNAs and proteins that arise from gene expression. These mRNA and proteins interact with each other with various degrees of specificity. Some diffuse around the cell. Others are bound to cell membranes, interacting with molecules in the environment. Still others pass through cell membranes and mediate long range signals to other cells in a multi-cellular organism. These molecules and their interactions comprise a *gene regulatory network*. A typical gene regulatory network looks something like this:

The nodes of this network are proteins, their corresponding mRNAs, and protein/protein complexes. Nodes that are depicted as lying along vertical lines are associated with the cell/environment interfaces, while the others are free-floating and diffusible. Implied are genes, the DNA sequences which are transcribed into the mRNAs that translate into proteins. Edges between nodes represent individual molecular reactions, the protein/protein and protein/mRNA interactions through which the products of one gene affect those of another, though the lack of experimentally obtained information often implies that some reactions are not modeled at such a fine level of detail. These interactions can be inductive (the arrowheads), with an increase in the concentration of one leading to an increase in the other, or inhibitory (the filled circles), with an increase in one leading to a decrease in the other. A series of edges indicates a chain of such dependences, with cycles corresponding to feedback loops. The network structure is an abstraction of the system's chemical dynamics, describing the manifold ways in which one substance affects all the others to which it is connected. In practice, such GRNs are inferred from the biological literature on a given system and represent a distillation of the collective knowledge about a set of related biochemical reactions.

Genes can be viewed as nodes in the network, with input being proteins such as transcription factors, and outputs being the level of gene expression. The node itself can also be viewed as a function which can be obtained by combining basic functions upon the inputs (in the Boolean network described below these are Boolean functions, typically AND, OR, and NOT). These functions have been interpreted as performing a kind of information processing within the cell, which determines cellular behavior. The basic drivers within cells are concentrations of some proteins, which determine both spatial (location within the cell or tissue) and temporal (cell cycle or developmental stage) coordinates of the cell, as a kind of "cellular memory". The gene networks are only beginning to be understood, and it is a next step for biology to attempt to deduce the functions for each gene "node", to help understand the behavior of the system in increasing levels of complexity, from gene to signaling pathway, cell or tissue level (see systems biology).

Mathematical models of GRNs have been developed to capture the behavior of the system being modeled, and in some cases generate predictions corresponding with experimental observations. In some other cases, models have proven to make accurate novel predictions, which can be tested experimentally, thus suggesting new approaches to explore in an experiment that sometimes wouldn't be considered in the design of the protocol of an experimental laboratory. The most common modeling technique involves the use of coupled ordinary differential equations (ODEs). Several other promising modeling techniques have been used, including Boolean networks, Petri nets, Bayesian networks, graphical Gaussian models, Stochastic, and Process Calculi. Conversely, techniques have been proposed for generating models of GRNs that best explain a set of time series observations.

## Modelling

### Coupled ODEs

It is common to model such a network with a set of coupled ordinary differential equations (ODEs) or stochastic ODEs, describing the reaction kinetics of the constituent parts. Suppose that our regulatory network has  $N$  nodes, and let  $S_1(t), S_2(t), \dots, S_N(t)$  represent the concentrations of the  $N$  corresponding substances at time  $t$ .

Then the temporal evolution of the system can be described approximately by

$$\frac{dS_j}{dt} = f_j(S_1, S_2, \dots, S_N)$$

where the functions  $f_j$  express the dependence of  $S_j$  on the concentrations of other substances present in the cell.

The functions  $f_j$  are ultimately derived from basic principles of chemical kinetics or simple expressions derived from these e.g. Michaelis-Menten enzymatic kinetics. Hence, the functional forms of the  $f_j$  are usually chosen as low-order polynomials or Hill functions that serve as an ansatz for the real molecular dynamics. Such models are then studied using the mathematics of nonlinear dynamics. System-specific information, like reaction rate constants and sensitivities, are encoded as constant parameters<sup>[3]</sup>.

By solving for the fixed point of the system:

$$\frac{dS_j}{dt} = 0$$

for all  $j$ , one obtains (possibly several) concentration profiles of proteins and mRNAs that are theoretically sustainable (though not necessarily stable). Steady states of kinetic equations thus correspond to potential cell types, and oscillatory solutions to the above equation to naturally cyclic cell types. Mathematical stability of these attractors can usually be characterized by the sign of higher derivatives at critical points, and then correspond to biochemical stability of the concentration profile. Critical points and bifurcations in the equations correspond to critical cell states in which small state or parameter perturbations could switch the system between one of several stable differentiation fates. Trajectories correspond to the unfolding of biological pathways and transients of the equations to short-term biological events. For a more mathematical discussion, see the articles on nonlinearity, dynamical systems, bifurcation theory, and chaos theory.

### Boolean network

The following example illustrates how a Boolean network can model a GRN together with its gene products (the outputs) and the substances from the environment that affect it (the inputs). Stuart Kauffman was amongst the first biologists to use the metaphor of Boolean networks to model genetic regulatory networks.<sup>[4]</sup>

1. Each gene, each input, and each output is represented by a node in a directed graph in which there is an arrow from one node to another if and only if there is a causal link between the two nodes.
2. Each node in the graph can be in one of two states: on or off.
3. For a gene, "on" corresponds to the gene being expressed; for inputs and outputs, "on" corresponds to the substance being present.
4. Time is viewed as proceeding in discrete steps. At each step, the new state of a node is a Boolean function of the prior states of the nodes with arrows pointing towards it.

The validity of the model can be tested by comparing simulation results with time series observations.

## Continuous networks

Continuous network models of GRNs are an extension of the boolean networks described above. Nodes still represent genes and connections between them regulatory influences on gene expression. Genes in biological systems display a continuous range of activity levels and it has been argued that using a continuous representation captures several properties of gene regulatory networks not present in the Boolean model.<sup>[5]</sup> Formally most of these approaches are similar to an artificial neural network, as inputs to a node are summed up and the result serves as input to a sigmoid function, e.g.,<sup>[6]</sup> but proteins do often control gene expression in a synergistic, i.e. non-linear, way.<sup>[7]</sup> However there is now a continuous network model<sup>[8]</sup> that allows grouping of inputs to a node thus realizing another level of regulation. This model is formally closer to a higher order recurrent neural network. The same model has also been used to mimic the evolution of cellular differentiation<sup>[9]</sup> and even multicellular morphogenesis.<sup>[10]</sup>

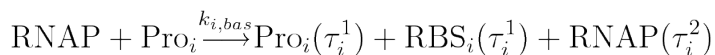
## Stochastic gene networks

Recent experimental results<sup>[11] [12]</sup> have demonstrated that gene expression is a stochastic process. Thus, many authors are now using the stochastic formalism, after the work by.<sup>[13]</sup> Works on single gene expression<sup>[14]</sup> and small synthetic genetic networks,<sup>[15] [16]</sup> such as the genetic toggle switch of Tim Gardner and Jim Collins, provided additional experimental data on the phenotypic variability and the stochastic nature of gene expression. The first versions of stochastic models of gene expression involved only instantaneous reactions and were driven by the Gillespie algorithm.<sup>[17]</sup>

Since some processes, such as gene transcription, involve many reactions and could not be correctly modeled as an instantaneous reaction in a single step, it was proposed to model these reactions as single step multiple delayed reactions in order to account for the time it takes for the entire process to be complete.<sup>[18]</sup>

From here, a set of reactions were proposed<sup>[19]</sup> that allow generating GRNs. These are then simulated using a modified version of the Gillespie algorithm, that can simulate multiple time delayed reactions (chemical reactions where each of the products is provided a time delay that determines when will it be released in the system as a "finished product").

For example, basic transcription of a gene can be represented by the following single-step reaction (RNAP is the RNA polymerase, RBS is the RNA ribosome binding site, and  $\text{Pro}_i$  is the promoter region of gene  $i$ ):



A recent work proposed a simulator (SGNSim, *Stochastic Gene Networks Simulator*),<sup>[20]</sup> that can model GRNs where transcription and translation are modeled as multiple time delayed events and its dynamics is driven by a stochastic simulation algorithm (SSA) able to deal with multiple time delayed events. The time delays can be drawn from several distributions and the reaction rates from complex functions or from physical parameters. SGNSim can generate ensembles of GRNs within a set of user-defined parameters, such as topology. It can also be used to model specific GRNs and systems of chemical reactions. Genetic perturbations such as gene deletions, gene over-expression, insertions, frame shift mutations can also be modeled as well.

The GRN is created from a graph with the desired topology, imposing in-degree and out-degree distributions. Gene promoter activities are affected by other genes expression products that act as inputs, in the form of monomers or combined into multimers and set as direct or indirect. Next, each direct input is assigned to an operator site and different transcription factors can be allowed, or not, to compete for the same operator site, while indirect inputs are given a target. Finally, a function is assigned to each gene, defining the gene's response to a combination of transcription factors (promoter state). The transfer functions (that is, how genes respond to a combination of inputs) can be assigned to each combination of promoter states as desired.

In other recent work, multiscale models of gene regulatory networks have been developed that focus on synthetic biology applications. Simulations have been used that model all biomolecular interactions in transcription,

translation, regulation, and induction of gene regulatory networks, guiding the design of synthetic systems.<sup>[21]</sup>

## Network connectivity

Empirical data indicate that biological gene networks are sparsely connected, and that the average number of upstream-regulators per gene is less than two.<sup>[22]</sup> Theoretical results show that selection for robust gene networks will favor minimally complex, more sparsely connected, networks.<sup>[22]</sup> These results suggest that a sparse, minimally connected, genetic architecture may be a fundamental design constraint shaping the evolution of gene network complexity.

## See also

- Operon
- Systems biology
- Synexpression
- Cis-regulatory module
- Body plan
- Morphogen

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## External links

- Gene Regulatory Networks <sup>[23]</sup> — Short introduction
  - BIB: Yeast Biological Interaction Browser <sup>[24]</sup>
  - Graphical Gaussian models for genome data <sup>[25]</sup> — Inference of gene association networks with GGMs
  - A bibliography on learning causal networks of gene interactions <sup>[26]</sup> - regularly updated, contains hundreds of links to papers from bioinformatics, statistics, machine learning.
  - <http://mips.gsf.de/proj/biorel/BIOREL> is a web-based resource for quantitative estimation of the gene network bias in relation to available database information about gene activity/function/properties/associations/interactio.
  - Evolving Biological Clocks using Genetic Regulatory Networks <sup>[27]</sup> - Information page with model source code and Java applet.
  - Engineered Gene Networks <sup>[28]</sup>
  - Tutorial: Genetic Algorithms and their Application to the Artificial Evolution of Genetic Regulatory Networks <sup>[29]</sup>
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## Organismic development

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**Morphogenesis** (from the Greek *morphê* shape and *genesis* creation, literally, "beginning of the shape"), is the biological process that causes an organism to develop its shape. It is one of three fundamental aspects of developmental biology along with the control of cell growth and cellular differentiation. The process controls the organized spatial distribution of cells during the embryonic development of an organism. Morphogenetic responses may be induced in organisms by hormones, by environmental chemicals ranging from substances produced by other organisms to toxic chemicals or radionuclides released as pollutants, and other plants, or by mechanical stresses induced by spatial patterning of the cells. Morphogenesis can take place in an embryo, a mature organism, in cell culture or inside tumor cell masses.

Morphogenesis also describes the development of unicellular life forms that do not have an embryonic stage in their life cycle, or describes the evolution of a body structure within a taxonomic group.

### History

Some of the earliest ideas on how physical and mathematical processes and constraints affect biological growth were written by D'Arcy Wentworth Thompson and Alan Turing. These works postulated the presence of chemical signals and physico-chemical processes such as diffusion, activation, and deactivation in cellular and organismic growth. The fuller understanding of the mechanisms involved in actual organisms required the discovery of DNA and the development of molecular biology and biochemistry.

### Molecular basis

Several types of molecules are particularly important during morphogenesis. Morphogens are soluble molecules that can diffuse and carry signals that control cell differentiation decisions in a concentration-dependent fashion. Morphogens typically act through binding to specific protein receptors. An important class of molecules involved in morphogenesis are transcription factor proteins that determine the fate of cells by interacting with DNA. These can be coded for by master regulatory genes and either activate or deactivate the transcription of other genes; in turn, these secondary gene products can regulate the expression of still other genes in a regulatory cascade. Another class of molecules involved in morphogenesis are molecules that control cell adhesion. For example, during gastrulation, clumps of stem cells switch off their cell-to-cell adhesion, become migratory, and take up new positions within an embryo where they again activate specific cell adhesion proteins and form new tissues and organs. Several examples that illustrate the roles of morphogens, transcription factors and cell adhesion molecules in morphogenesis are discussed below.

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## Cellular basis

Morphogenesis arises because of changes in the cellular structure or how cells interact in tissues<sup>[1]</sup>. Certain cell types "sort out". Cell "sorting out" means that when the cells physically interact they move so as to sort into clusters that maximize contact between cells of the same type. The ability of cells to do this comes from differential cell adhesion. Two well-studied types of cells that sort out are epithelial cells and mesenchymal cells. During embryonic development there are some cellular differentiation events during which mesenchymal cells become epithelial cells and at other times epithelial cells differentiate into mesenchymal cells (see Epithelial-mesenchymal transition). Following epithelial-mesenchymal transition, cells can migrate away from an epithelium and then associate with other similar cells in a new location.

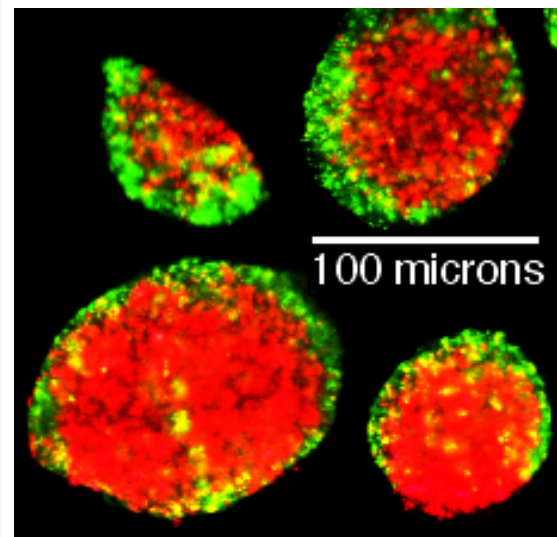
## Adhesion

During embryonic development, cells are restricted to different layers due to differential affinities. One of the ways this can occur is when cells share the same cell-to-cell adhesion molecules. For instance, homotypic cell adhesion can maintain boundaries between groups of cells that have different adhesion molecules. Furthermore, cells can sort based upon differences in adhesion between the cells, so even two populations of cells with different levels of the same adhesion molecule can sort out. In cell culture cells that have the strongest adhesion move to the center of a mixed aggregates of cells.

The molecules responsible for adhesion are called **cell adhesion molecules (CAMs)**. Several types of cell adhesion molecules are known and one major class of these molecules are cadherins. There are dozens of different cadherins that are expressed on different cell types. Cadherins bind to other cadherins in a like-to-like manner: E-cadherin (found on many epithelial cells) binds preferentially to other E-cadherin molecules. Mesenchymal cells usually express other cadherin types such as N-cadherin.

## Extracellular matrix

The extracellular matrix (ECM) is involved with separating tissues, providing structural support or providing a structure for cells to migrate on. Collagen, laminin, and fibronectin are major ECM molecules that are secreted and assembled into sheets, fibers, and gels. Multisubunit transmembrane receptors called integrins are used to bind to the ECM. Integrins bind extracellularly to fibronectin, laminin, or other ECM components, and intracellularly to microfilament-binding proteins  $\alpha$ -actinin and talin to link the cytoskeleton with the outside. Integrins also serve as receptors to trigger signal transduction cascades when binding to the ECM. A well-studied example of morphogenesis that involves ECM is mammary gland ductal branching<sup>[2]</sup>,<sup>[3]</sup>.



Example of cell sorting out with cultured P19 embryonal carcinoma cells. Live cells were stained with either DiI (red) or DiO (green). The red cells were genetically altered and express higher levels of E-cadherin than the green cells. After labeling, the two populations of cells were mixed and cultured together allowing the cells to form large multi-cellular mixed aggregates. Individual cells are less than 10 micrometres in diameter. The image was captured by scanning confocal microscopy.



## See also

- Embryogenesis
- Pattern formation
- French flag model
- Reaction-diffusion
- Neurulation
- Gastrulation
- Axon guidance
- Eye development
- Polycystic kidney disease 2
- Drosophila embryogenesis

## External links

- Artificial Life model of multicellular morphogenesis with autonomously generated gradients for positional information <sup>[4]</sup>

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# Organization

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An **organization** (or **organisation** — see spelling differences) is a social arrangement which pursues collective goals, controls its own performance, and has a boundary separating it from its environment. The word itself is derived from the Greek word *ὄργανον* (organon [itself derived from the better-known word *ἐργον* ergon - work; deed - > ergonomics, etc]) meaning *tool*.

In the social sciences, organizations are studied by researchers from several disciplines, the most common of which are sociology, economics, political science, psychology, management, and organizational communication. The broad area is commonly referred to as organizational studies, organizational behavior or organization analysis. Therefore, a number of different theories and perspectives exist, some of which are compatible,

- Organization – process-related: an entity is being (re-)organized (organization as task or action).
- Organization – functional: organization as a function of how entities like businesses or state authorities are used (organization as a permanent structure).
- Organization – institutional: an entity is an organization (organization as an actual purposeful structure within a social context)

## Organization in sociology

In sociology "organization" is understood as planned, coordinated and purposeful action of human beings to construct or compile a common tangible or intangible product. This action is usually framed by formal membership and form (institutional rules). Sociology distinguishes the term organization into planned formal and unplanned informal (i.e. spontaneously formed) organizations. Sociology analyzes organizations in the first line from an institutional perspective. In this sense, organization is a permanent arrangement of elements. These elements and their actions are determined by rules so that a certain task can be fulfilled through a system of coordinated division of labor.

An organization is defined by the elements that are part of it (who belongs to the organization and who does not?), its communication (which elements communicate and how do they communicate?), its autonomy (Max Weber termed autonomy in this context: Autocephaly)(which changes are executed autonomously by the organization or its elements?), and its rules of action compared to outside events (what causes an organization to act as a collective actor?).

By coordinated and planned cooperation of the elements, the organization is able to solve tasks that lie beyond the abilities of the single elements. The price paid by the elements is the limitation of the degrees of freedom of the elements. Advantages of organizations are enhancement (more of the same), addition (combination of different features) and extension. Disadvantages can be inertness (through co-ordination) and loss of interaction.

## Organization in management and organizational studies

Management is interested in organization mainly from an instrumental point of view. For a company, organization is a means to an end to achieve its goals.

## Organization theories

Among the theories that are or have been most influential are:

- Weberian organization theory (refer to Max Weber's chapter on Bureaucracy in his book 'Economy and Society')
  - Marxist organization analysis
  - Scientific management (mainly following Frederick W. Taylor)
  - Human Relations Studies (going back to the Hawthorne studies, Maslow and Herzberg)
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- Administrative theories (with work by e.g. Henri Fayol and Chester Barnard)
- Contingency theory
- New institutionalism and new institutional economics
- Network analysis
- Economic sociology
- Organization ecology (or demography of organizations)
- Agency theory (sometimes called principal - agent theory)
- Studies of organization culture
- Labour Process Theory
- Critical Management Studies
- Complexity Theory and Organizations
- Transaction cost theory/Transaction cost Economics (TCE)
- Garbage can model
- Actor-Network Theory and the 'Montreal School'
- social entrepreneurship

## Organizational structures

The study of organizations includes a focus on optimizing organizational structure. According to management science, most human organizations fall roughly into four types:

- Pyramids or hierarchies
- Committees or juries
- Matrix organizations
- Ecologies

### Pyramids or hierarchies

A hierarchy exemplifies an arrangement with a leader who leads leaders. This arrangement is often associated with bureaucracy. Hierarchies were satirized in *The Peter Principle* (1969), a book that introduced *hierarchiology* and the saying that "in a hierarchy every employee tends to rise to his level of incompetence".

An extremely rigid, in terms of responsibilities, type of organization is exemplified by Führerprinzip.

### Committees or juries

These consist of a group of peers who decide as a group, perhaps by voting. The difference between a jury and a committee is that the members of the committee are usually assigned to perform or lead further actions after the group comes to a decision, whereas members of a jury come to a decision. In common law countries legal juries render decisions of guilt, liability and quantify damages; juries are also used in athletic contests, book awards and similar activities. Sometimes a selection committee functions like a jury. In the Middle Ages juries in continental Europe were used to determine the law according to consensus amongst local notables.

Committees are often the most reliable way to make decisions. Condorcet's jury theorem proved that if the average member votes better than a roll of dice, then adding more members increases the number of majorities that can come to a correct vote (however correctness is defined). The problem is that if the average member is *worse* than a roll of dice, the committee's decisions grow worse, not better: Staffing is crucial.

Parliamentary procedure, such as Robert's Rules of Order, helps prevent committees from engaging in lengthy discussions without reaching decisions.

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### Staff organization or cross-functional team

A staff helps an expert get all his work done. To this end, a "chief of staff" decides whether an assignment is routine or not. If it's routine, he assigns it to a staff member, who is a sort of junior expert. The chief of staff schedules the routine problems, and checks that they are completed.

If a problem is not routine, the chief of staff notices. He passes it to the expert, who solves the problem, and educates the staff – converting the problem into a routine problem.

In a "cross functional team", like an executive committee, the boss *has* to be a non-expert, because so many kinds of expertise are required.

### Organization: Cyclical structure

A theory put forth by renowned scholar Stephen John has asserted that throughout the cyclical nature of one's life organizational patterns are key to success. Through various social and political constraints within society one must realize that organizational skills are paramount to success. Stephen John suggests that emphasis needs to be put on areas such as individual/ group processes, functionality, and overall structures of institutions in order to maintain a proper organization. Furthermore, the individual's overall organizational skills are pre-determined by the processes undertaken.:

### Matrix organization

This organizational type assigns each worker two bosses in two different hierarchies. One hierarchy is "functional" and assures that each type of expert in the organization is well-trained, and measured by a boss who is super-expert in the same field. The other direction is "executive" and tries to get projects completed using the experts. Projects might be *organized by regions, customer types, or some other schema*. matrix management

### Ecologies

This organization has intense competition. Bad parts of the organization starve. Good ones get more work. Everybody is paid for what they actually do, and runs a tiny business that has to show a profit, or they are fired.

Companies who utilize this organization type reflect a rather one-sided view of what goes on in ecology. It is also the case that a natural ecosystem has a natural border - ecoregions do not in general compete with one another in any way, but are very autonomous.

The pharmaceutical company GlaxoSmithKline talks about functioning as this type of organization in this external article <sup>[1]</sup> from The Guardian.

### "Chaordic" organizations

The chaordic model of organizing human endeavors emerged in the 1990s, based on a blending of chaos and order (hence "chaordic"), comes out of the work of Dee Hock and the creation of the VISA financial network. Blending democracy, complex system, consensus decision making, co-operation and competition, the chaordic approach attempts to encourage organizations to evolve from the increasingly nonviable hierarchical, command-and-control models.

Similarly, emergent organizations, and the principle of self-organization. See also group entity for an anarchist perspective on human organizations.

Organizations that are legal entities: government, international organization, non-governmental organization, armed forces, corporation, partnership, charity, not-for-profit corporation, cooperative, university.

## The organization of the artist

The organization of the artist is a term first used by architect Frank Gehry to denote the organizational set-up he enforces in order to ensure that the architect/artist is in control of design through construction. The organization of the artist deliberately eliminates the influence of politicians and business people on design. The purpose of the organization of the artist is to ensure that it is the design of the architect/artist that is actually implemented and not some compromise decided by political and business interests.

Gehry initially developed the concept of the organization of the artist as a reaction against what he calls the "marginalization of the architect/artist." Gehry explains:

"There's a tendency to marginalize and treat the creative people like women are treated, 'sweetie, us big business guys know how to do this, just give us the design and we'll take it from there.' That is the worst thing that can happen. It requires the organization of the artist to prevail so that the end product is as close as possible to the object of desire [the design] that both the client and architect have come to agree on." (Flyvbjerg 2005, 53).

Gehry argues that the organization of the artist, in addition to making possible artistic integrity, also helps keep his buildings on time and budget, which is rare for the type of innovative and complex designs that Gehry is known for. The organization of the artist thus serves the dual purpose of artistic freedom and economic prudence.

## Leadership in organizations

### Leadership in formal organizations

An organization that is established as an instrument or means for achieving defined objectives has been referred to as a **formal organization**. Its design specifies how goals are subdivided and reflected in subdivisions of the organization. Divisions, departments, sections, positions, jobs, and tasks make up this work structure. Thus, the formal organization is expected to behave impersonally in regard to relationships with clients or with its members. According to Weber's definition, entry and subsequent advancement is by merit or seniority. Each employee receives a salary and enjoys a degree of tenure that safeguards him from the arbitrary influence of superiors or of powerful clients. The higher his position in the hierarchy, the greater his presumed expertise in adjudicating problems that may arise in the course of the work carried out at lower levels of the organization. It is this bureaucratic structure that forms the basis for the appointment of heads or chiefs of administrative subdivisions in the organization and endows them with the authority attached to their position.<sup>[2]</sup>

### Leadership in informal organizations

In contrast to the appointed head or chief of an administrative unit, a leader emerges within the context of the **informal organization** that underlies the formal structure. The informal organization expresses the personal objectives and goals of the individual membership. Their objectives and goals may or may not coincide with those of the formal organization. The informal organization represents an extension of the social structures that generally characterize human life — the spontaneous emergence of groups and organizations as ends in themselves.<sup>[2]</sup>

In prehistoric times, man was preoccupied with his personal security, maintenance, protection, and survival. Now man spends a major portion of his waking hours working for organizations. His need to identify with a community that provides security, protection, maintenance, and a feeling of belonging continues unchanged from prehistoric times. This need is met by the informal organization and its emergent, or unofficial, leaders.<sup>[3]</sup>

Leaders emerge from within the structure of the informal organization. Their personal qualities, the demands of the situation, or a combination of these and other factors attract followers who accept their leadership within one or several overlay structures. Instead of the authority of position held by an appointed head or chief, the emergent leader wields influence or power. Influence is the ability of a person to gain cooperation from others by means of

persuasion or control over rewards. Power is a stronger form of influence because it reflects a person's ability to enforce action through the control of a means of punishment.<sup>[3]</sup>

### **Leader in organizations**

An individual who is appointed to a managerial position has the right to command and enforce obedience by virtue of the authority of his position. However, he must possess adequate personal attributes to match his authority, because authority is only potentially available to him. In the absence of sufficient personal competence, a manager may be confronted by an emergent leader who can challenge his role in the organization and reduce it to that of a figurehead. However, only authority of position has the backing of formal sanctions. It follows that whoever wields personal influence and power can legitimize this only by gaining a formal position in the hierarchy, with commensurate authority.<sup>[3]</sup>

### **Hybrid organizations**

A hybrid organization is a body that operates in both the public sector and the private sector, simultaneously fulfilling public duties and developing commercial market activities. As a result the hybrid organization becomes a mixture of both a part of government and a private corporation.

### **See also**

- Affinity group
  - Bureaucracy
  - Business organization
  - Charitable trust
  - Coalition
  - Collective
  - Cooperative
  - Hybrid organization
  - International organization
  - Mutual organization
  - Non-governmental organization
  - Organizational culture
  - Organization design
  - Organizational climate
  - Organizational development
  - Organization of the artist
  - Organization studies
  - Pacifist organization
  - Requisite organization
  - Service organization
  - Size of groups, organizations, and communities
  - Strategic management
  - Strategic planning
  - Terrorist organizations
  - Umbrella organization
  - Virtual organization
  - Voluntary association
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## Related lists

- List of environmental organizations
- List of trade unions
- List of civic, fraternal, service, and professional organizations
- List of professional organizations

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## External links

- Research on Organizations: Bibliography Database and Maps <sup>[10]</sup>
- TheTransitioner.org <sup>[11]</sup>: a site dedicated to collective intelligence and structure of organizations
- Principles of Organization <sup>[12]</sup>

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- [8] <http://worldcat.org/oclc/1329335>
- [9] <http://worldcat.org/oclc/154085959>
- [10] <http://ot.cavarretta.com>

[11] <http://www.thetransitioner.org>

[12] <http://www.cognobytes.com/mgmt/ob/principle-of-organization>

## Two-factor theory of nerve impulse

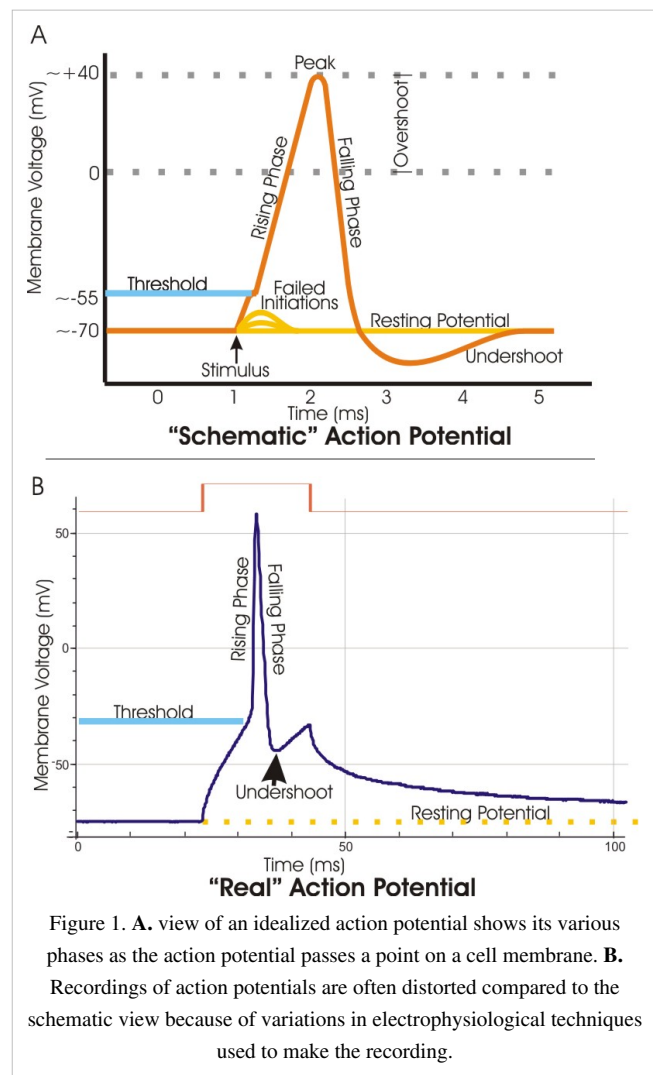
An **action potential** (or **nerve impulse**) is a transient alteration of the transmembrane voltage (or membrane potential) across an excitable membrane in an excitable cell (such as a neuron or myocyte) generated by the activity of voltage-gated ion channels embedded in the membrane. The best known action potentials are pulse-like waves of voltage that travel along the axons of neurons.<sup>[1]</sup>

### Overview

A typical action potential is initiated at the axon hillock when the membrane is depolarized sufficiently (i.e. when its voltage is increased sufficiently). As the membrane potential is increased, sodium ion channels open, allowing the entry of sodium ions into the cell. This is followed by the opening of potassium ion channels that permit the exit of potassium ions from the cell. The inward flow of sodium ions increases the concentration of positively-charged cations in the cell and causes depolarization, where the potential of the cell is higher than the cell's resting potential. The sodium channels close at the peak of the action potential, while potassium continues to leave the cell. The efflux of potassium ions decreases the membrane potential or hyperpolarizes the cell. For small voltage increases from rest, the potassium current exceeds the sodium current and the voltage returns to its normal resting value, typically  $-70$  mV.<sup>[2]</sup> However, if the voltage increases past a critical threshold, typically  $15$  mV higher than the resting value, the sodium current dominates. This results in a runaway condition whereby the positive feedback from the sodium current activates even more sodium channels. Thus, the cell "fires," producing an action potential.<sup>[3]</sup>

[4]

Currents produced by the opening of voltage-gated channels in the course of an action potential are typically significantly larger than the initial stimulating current. Thus the amplitude, duration, and shape of the action potential are largely determined by the properties of the excitable membrane and not the amplitude or duration of the stimulus. This all-or-nothing property of action potential sets it apart from graded potentials such as receptor potentials, electrotonic potentials, and synaptic potentials, which do scale with the magnitude of the stimulus. A variety of action potential types exist in many cell types and cell compartments as determined by the types of voltage-gated channels, leak channels, channel distributions, ionic concentrations, membrane capacitance, temperature, and other factors.





The principal ions involved in an action potential are sodium and potassium cations; sodium ions enter the cell, and potassium ions leave, restoring equilibrium. Relatively few ions need to cross the membrane for the membrane voltage to change drastically. The ions exchanged during an action potential, therefore, make a negligible change in the interior and exterior ionic concentrations. The few ions that do cross are pumped out again by the continual action of the sodium–potassium pump, which, with other ion transporters, maintains the normal ratio of ion concentrations across the membrane. Calcium cations and chloride anions are involved in a few types of action potentials, such as the cardiac action potential and the action potential in the single-celled alga *Acetabularia*, respectively.

Although action potentials are generated locally on patches of excitable membrane, the resulting currents can trigger action potentials on neighboring stretches of membrane, precipitating a domino-like propagation. In contrast to passive spread of electric potentials (electrotonic potential), action potentials are generated anew along excitable stretches of membrane and propagate without decay.<sup>[5]</sup> Myelinated sections of axons are not excitable and do not produce action potentials and the signal is propagated passively as electrotonic potential. Regularly spaced unmyelinated patches, called the nodes of Ranvier, generate action potentials to boost the signal. Known as saltatory conduction, this type of signal propagation provides a favorable tradeoff of signal velocity and axon diameter. Depolarization of axon terminals generally triggers the release of neurotransmitter into the synaptic cleft. Additionally, backpropagating action potentials have been recorded in the dendrites of pyramidal neurons, which are ubiquitous in the neocortex.<sup>[6]</sup> These are thought to have a role in spike-timing-dependent plasticity.

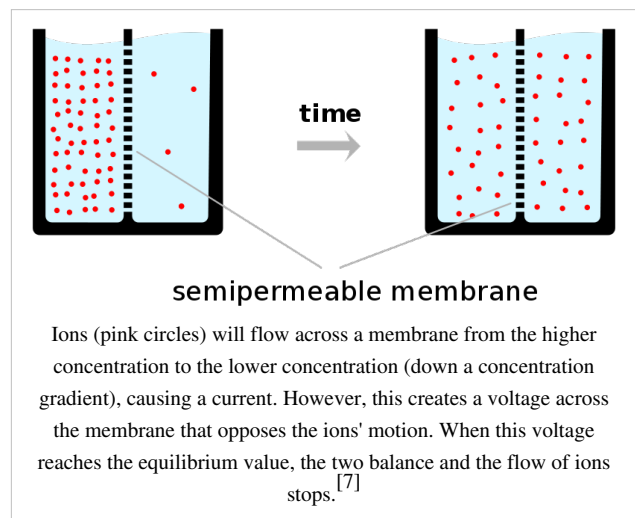
## Biophysical and cellular context

### Ions and the forces driving their motion

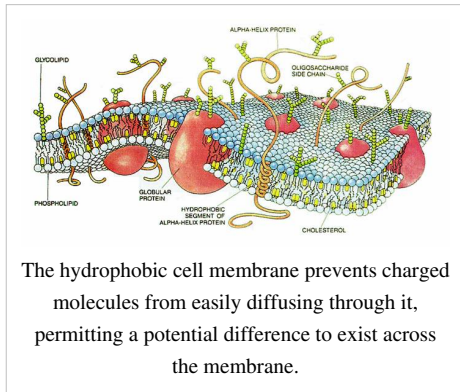
Electrical signals within biological organisms are generally driven by ions.<sup>[8]</sup> The most important cations for the action potential are sodium ( $\text{Na}^+$ ) and potassium ( $\text{K}^+$ ).<sup>[9]</sup> Both of these are *monovalent* cations that carry a single positive charge. Action potentials can also involve calcium ( $\text{Ca}^{2+}$ ),<sup>[10]</sup> which is a *divalent* cation that carries a double positive charge. The chloride anion ( $\text{Cl}^-$ ) plays a major role in the action potentials of some algae,<sup>[11]</sup> but plays a negligible role in the action potentials of most animals.<sup>[12]</sup>

Ions cross the cell membrane under two influences: diffusion and electric fields. Let's start off with a simple example whereby two solutions are separated by a porous barrier. Let us further call these two solutions A and B. In this case, diffusion will ensure that they will eventually mix into equal solutions. This mixing occurs because of the difference in their concentrations. The region with high concentration will diffuse out towards the region with low concentration. To further the example, let solution A have 30 sodium ions and 30 chloride ions. Also, let solution B have only 20 sodium ions and 20 chloride ions. Assuming the barrier allows both types of ions to travel through it, then a steady state will be reached whereby both solutions have 25 sodium ions and 25 chloride ions. If, however, the porous barrier is selective to which ions are let through, then diffusion alone will not determine the resulting solution. Returning to the previous example, let's now construct a barrier that is only permeable to sodium ions. Since solution B has a lower concentration of both sodium and chloride, it will attract both ions from solution A. However, only sodium will travel through the barrier.

This will result in an accumulation of sodium in solution B. Since sodium has a positive charge, this accumulation will make solution B more positive relative to solution A. Positive sodium ions will be less likely to travel to the now



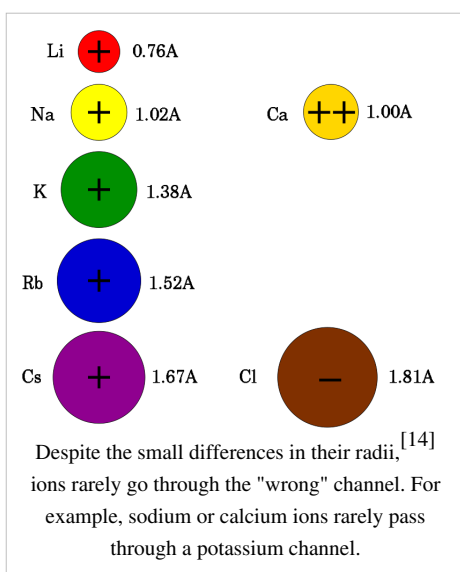
more positive B solution. This constitutes the second factor controlling ion flow, namely electric fields. The point at which this electric field completely counteracts the force due to diffusion is called the equilibrium potential. At this point, the net flow of this specific ion (in this case sodium) is zero.



## Cell membrane

Each neuron is encased in a cell membrane, made of a phospholipid bilayer. This membrane is nearly impermeable to ions.<sup>[13]</sup> To transfer ions into and out of the neuron, the membrane provides two structures. Ion pumps use the cell's energy to continuously move ions in and out. They create concentration differences (between the inside and outside of the neuron) by transporting ions against their concentration gradients (from regions of low concentration to regions of high concentration). The ion channels then use this concentration difference to transport ions down their concentration gradients (from regions of

high concentration to regions of low concentration). However, unlike the continuous transport by the ion pumps, the transport by the ion channels is non continuous. They only open and close in response to signals from their environment. This transport of ions through the ion channels then changes the voltage of the cell membrane. These changes are what bring about an action potential. As an analogy, ion pumps play the role of the battery that allows a radio circuit (the ion channels) to transmit a signal (action potential).<sup>[1]</sup>



## Membrane potential

The cell membrane acts as a barrier which prevents the inside solution (intracellular fluid) from mixing with the outside solution (extracellular fluid). These two solutions have different concentrations of their ions. Furthermore, this difference in concentrations leads to a difference in charge of the solutions. This creates a situation whereby one solution is more positive than the other. Therefore, positive ions will tend to gravitate towards the negative solution. Likewise, negative ions will tend to gravitate towards the positive solution. To quantify this property, one would like to somehow capture this relative positivity (or negativity). To do this, the outside solution is set as the zero voltage. Then the difference between the inside voltage and the zero voltage is determined. For example, if the outside voltage is 100 mV, and the inside voltage is 30 mV, then the difference is 70 mV. This difference is what is commonly referred to as the membrane potential.

## Ion channels

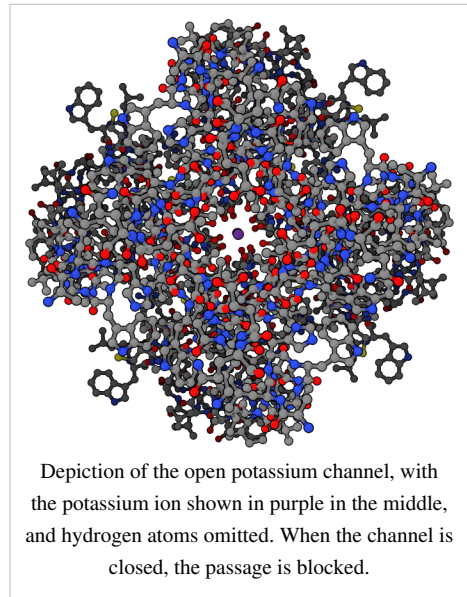
Ion channels are integral membrane proteins with a pore through which ions can travel between extracellular space and cell interior. Most channels are specific (selective) for one ion; for example, most potassium channels are characterized by 1000:1 selectivity ratio for potassium over sodium, though potassium and sodium ions have the same charge and differ only slightly in their radius. The channel pore is typically so small that ions must pass through it in single-file order.<sup>[15] [16]</sup> Channel pore can be either open or closed for ion passage, although a number of channels demonstrate various sub-conductance levels. When a channel is open, ions permeate through the channel pore down the transmembrane concentration gradient for that particular ion. Rate of ionic flow through the channel, i.e. single-channel current amplitude, is determined by the maximum channel conductance and electrochemical driving force for that ion, which is the difference between instantaneous value of the membrane potential and the

value of the reversal potential.<sup>[17]</sup>

The action potential is a manifestation of different ion channels opening and closing at different times.<sup>[18]</sup>

A channel may have several different states (corresponding to different conformations of the protein), but each such state is either open or closed. In general, closed states correspond either to a contraction of the pore—making it impassable to the ion—or to a separate part of the protein stoppering the pore. For example, the voltage-dependent sodium channel undergoes *inactivation*, in which a portion of the protein swings into the pore, sealing it.<sup>[19]</sup> This inactivation shuts off the sodium current and plays a critical role in the action potential.

Ion channels can be classified by how they respond to their environment.<sup>[20]</sup> For example, the ion channels involved in the action potential are *voltage-sensitive channels*; they open and close in response to the voltage across the membrane. *Ligand-gated channels* form another important class; these ion channels open and close in response to the binding of a ligand molecule, such as a neurotransmitter. Other ion channels open and close with mechanical forces. Still other ion channels—such as those of sensory neurons—open and close in response to other stimuli, such as light, temperature or pressure.



## Ion pumps

The ionic currents of the action potential flow in response to concentration differences of the ions across the cell membrane. These concentration differences are established by ion pumps, which are integral membrane proteins that carry out active transport, i.e., use cellular energy (ATP) to "pump" the ions against their concentration gradient.<sup>[21]</sup> Such ion pumps take in ions from one side of the membrane (decreasing its concentration there) and release them on the other side (increasing its concentration there). The ion pump most relevant to the action potential is the sodium–potassium pump, which transports three sodium ions out of the cell and two potassium ions in.<sup>[22]</sup> Consequently, the concentration of potassium ions  $K^+$  inside the neuron is roughly 20-fold larger than the outside concentration, whereas the sodium concentration outside is roughly ninefold larger than inside.<sup>[23] [24]</sup> Similarly, other ions have different concentrations inside and outside the neuron, such as calcium, chloride and magnesium.<sup>[24]</sup>

Ion pumps influence the action potential only by establishing the relative ratio of intracellular and extracellular ion concentrations. The action potential mainly involves the opening and closing of ion channels, not ion pumps. If the ion pumps are turned off by removing their energy source, or by adding an inhibitor such as ouabain, the axon can still fire hundreds of thousands of action potentials before their amplitudes begin to decay significantly.<sup>[21]</sup> In particular, ion pumps play no significant role in the repolarization of the membrane after an action potential.<sup>[9]</sup>

## Resting potential

As described in the section Ions and the forces driving their motion, equilibrium or reversal potential of an ion is the value of transmembrane voltage at which the electric force generated by diffusional movement of the ion down its concentration gradient becomes equal to the molecular force of that diffusion. The equilibrium potential for any ion can be calculated using the Nernst equation.<sup>[25] [26]</sup> For example, reversal potential for potassium ions will be as follows

$$E_{eq,K^+} = \frac{RT}{zF} \ln \frac{[K^+]_o}{[K^+]_i},$$

where

- $E_{eq,K^+}$  is the equilibrium potential for potassium, measured in volts
- $R$  is the universal gas constant, equal to  $8.314 \text{ joules} \cdot \text{K}^{-1} \cdot \text{mol}^{-1}$
- $T$  is the absolute temperature, measured in kelvins ( $= K = \text{degrees Celsius} + 273.15$ )
- $z$  is the number of elementary charges of the ion in question involved in the reaction
- $F$  is the Faraday constant, equal to  $96,485 \text{ coulombs} \cdot \text{mol}^{-1}$  or  $\text{J} \cdot \text{V}^{-1} \cdot \text{mol}^{-1}$
- $[K^+]_o$  is the extracellular concentration of potassium, measured in  $\text{mol} \cdot \text{m}^{-3}$  or  $\text{mmol} \cdot \text{l}^{-1}$
- $[K^+]_i$  is the intracellular concentration of potassium.

Even if two different ions have the same charge (ie.  $K^+$  and  $Na^+$ ), they can still have very different equilibrium potentials, provided their outside and/or inside concentrations differ. Take, for example, the equilibrium potentials of potassium and sodium in neurons. The potassium equilibrium potential  $E_K$  is  $-84 \text{ mV}$  with  $5 \text{ mM}$  potassium outside and  $140 \text{ mM}$  inside. The sodium equilibrium potential, on the other hand,  $E_{Na}$  is approximately  $+40 \text{ mV}$  with  $1\text{-}2 \text{ mM}$  sodium inside and  $120 \text{ mM}$  outside.<sup>[27]</sup>

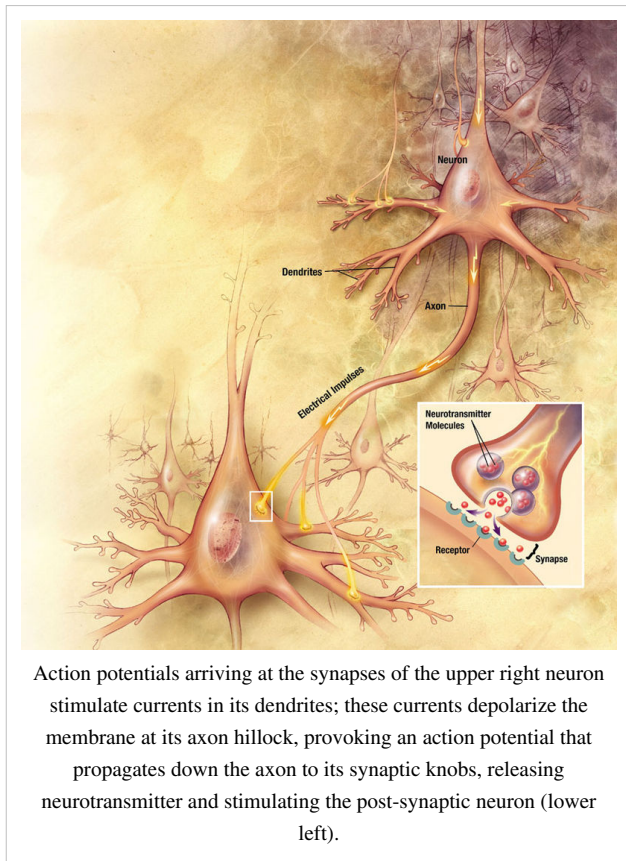
However, there is an equilibrium membrane potential  $E_m$  at which the *net* flow of all ions across the membrane is zero. This potential is calculated by the Goldman equation<sup>[28] [29]</sup> It is essentially the Nernst equation, in that it is based on the charges of the ions in question, as well as the difference between their inside and outside concentrations. However, it also takes into consideration the relative permeability of the plasma membrane to each ion in question.

$$E_m = \frac{RT}{F} \ln \left( \frac{P_K[K^+]_{out} + P_{Na}[Na^+]_{out} + P_{Cl}[Cl^-]_{in}}{P_K[K^+]_{in} + P_{Na}[Na^+]_{in} + P_{Cl}[Cl^-]_{out}} \right)$$

for the three monovalent ions most important to action potentials: potassium ( $K^+$ ), sodium ( $Na^+$ ), and chloride ( $Cl^-$ ). Being an anion, the chloride terms are treated differently than the cation terms; the inside concentration is in the numerator, and the outside concentration is in the denominator, which is reversed from the cation terms.  $P_i$  stands for the permeability of the ion type  $i$ . If calcium ions are also considered, which are critically important for action potentials in muscles, the formula for the equilibrium potential becomes more complicated.<sup>[30]</sup>

Generation of resting membrane potential is explicitly explained by the Goldman equation. The resting plasma membrane of most animal cells is much more permeable to  $K^+$ , which results in the resting potential  $V_{rest}$  to be close to the potassium equilibrium potential.<sup>[31] [32] [33]</sup>

It is important to realize, that ionic and water permeability of a pure lipid bilayer is very small, and it is similarly negligible for ions of comparable size, such as  $Na^+$  and  $K^+$ . The cell membranes, however, contain a large number of ion channels, water channels (aquaporins), and various ionic pumps, exchangers, and transporters, which dramatically and selectively increase permeability of the membrane for different ions. The relatively high membrane permeability for potassium ions at resting potential results from Inward-rectifier potassium ion channels which are open at negative voltages, and so called leak potassium conductances such as open rectifier  $K^+$  channel (ORK<sup>+</sup>) which are locked in open state. These potassium channels should not be confused with voltage-activated  $K^+$  channels responsible for membrane repolarization during action potential.



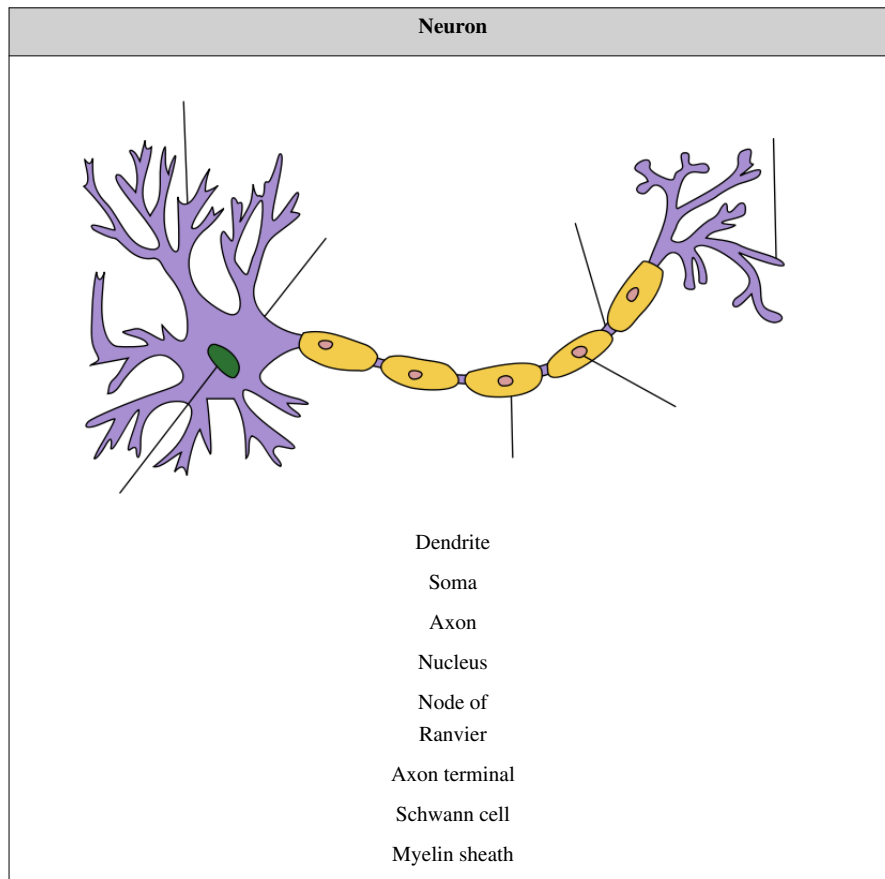
## Anatomy of a neuron

Several types of cells support an action potential, such as plant cells, muscle cells, and the specialized cells of the heart (in which occurs the cardiac action potential). However, the main excitable cell is the neuron, which also has the simplest mechanism for the action potential.

Neurons are electrically excitable cells generally composed of one or more dendrites, a single soma, a single axon and one or more axon terminals. The dendrite is one of the two types of synapses, the other being the axon terminal buttons. Dendrites form protrusions in response to the axon terminal boutons. These protrusions, or spines, are designed to capture the neurotransmitters released by the presynaptic neuron. They have a high concentration of ligand activated channels. It is, therefore, here where synapses from two neurons communicate with one another. These spines have a thin neck connecting a bulbous protrusion to the main dendrite. This ensures that changes occurring inside the spine are less likely to affect the neighbouring spines. The dendritic spine can,

therefore, with rare exception (see LTP), act as an independent unit. The dendrites then connect onto the soma. The soma houses the nucleus, which acts as the regulator for the neuron. Unlike the spines, the surface of the soma is populated by voltage activated ion channels. These channels help transmit the signals generated by the dendrites. Emerging out from the soma is the axon hillock. This region is characterized by having an incredibly high concentration of voltage activated sodium channels. It is generally considered to be the spike initiation zone for action potentials.<sup>[34]</sup> Multiple signals generated at the spines, and transmitted by the soma all converge here. Immediately after the axon hillock is the axon. This is a thin tubular protrusion traveling away from the soma. The axon is insulated by a myelin sheath. Myelin is composed of Schwann cells that wrap themselves multiple times around the axonal segment. This forms a thick fatty layer that prevents ions from entering or escaping the axon. This insulation both prevents significant signal decay as well as ensuring faster signal speed. This insulation, however, has the restriction that no channels can be present on the surface of the axon. There are, therefore, regularly spaced patches of membrane which have no insulation. These nodes of ranvier can be considered to be 'mini axon hillocks' as their purpose is to boost the signal in order to prevent significant signal decay. At the furthest end, the axon loses its insulation and begins to branch into several axon terminals. These axon terminals then end in the form the second class of synapses, axon terminal buttons. These buttons have voltage activated calcium channels which come into play when signaling other neurons.

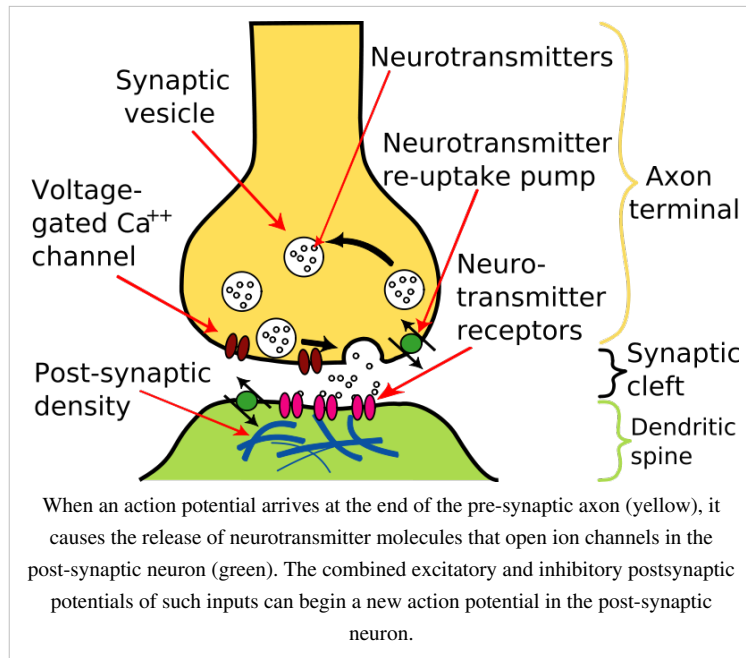
### Structure of a typical neuron





## Initiation

Before considering the propagation of action potentials along axons and their termination at the synaptic knobs, it is helpful to consider the methods by which action potentials can be initiated at the axon hillock. The basic requirement is that the membrane voltage at the hillock be raised above the threshold for firing.<sup>[1]</sup> There are several ways in which this depolarization can occur.



## Neurotransmission

Action potentials are most commonly initiated by excitatory postsynaptic potentials from a presynaptic neuron.<sup>[35]</sup> Typically, neurotransmitter molecules are released by the presynaptic neuron. These neurotransmitters then bind to receptors on the postsynaptic cell. This binding opens various types of ion channels. This opening has the further effect of changing the local permeability of the cell membrane and thus the membrane potential. If the binding increases the voltage (depolarizes the membrane), the synapse is excitatory. If, however, the binding decreases the voltage (hyperpolarizes the membrane), it is inhibitory. Whether the voltage is decreased

or increased, the change propagates passively to nearby regions of the membrane (as described by the cable equation and its refinements). Typically, the voltage stimulus decays exponentially with the distance from the synapse and with time from the binding of the neurotransmitter. Some fraction of an excitatory voltage may reach the axon hillock and may (in rare cases) depolarize the membrane enough to provoke a new action potential. More typically, the excitatory potentials from several synapses must work together at nearly the same time to provoke a new action potential. Their joint efforts can be thwarted, however, by the counter-acting inhibitory postsynaptic potentials.

Neurotransmission can also occur through electrical synapses.<sup>[36]</sup> Due to the direct connection between excitable cells in the form of gap junctions, an action potential can be transmitted directly from one cell to the next. The free flow of ions between cells enables rapid non-chemical mediated transmission. Rectifying channels ensure that action potentials only move in one direction through an electrical synapse. In the human nervous system this type of synapse is uncommon however.

## "All-or-none" principle

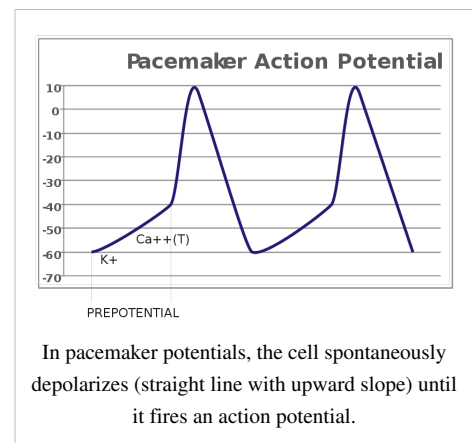
The amplitude of an action potential is independent of the amount of current which produced it. In other words, larger currents do not create larger action potentials. Therefore action potentials are said to be *all-or-none* (or boolean), since they either occur fully or they do not occur at all. Instead, the frequency of action potentials is what encodes for the intensity of a stimulus. This is in contrast to receptor potentials, whose amplitudes are dependent on the intensity of a stimulus.<sup>[1]</sup>

## Sensory neurons

In sensory neurons, an external signal such as pressure, temperature, light, or sound is coupled with the opening and closing of ion channels, which in turn alter the ionic permeabilities of the membrane and its voltage.<sup>[37]</sup> These voltage changes can again be excitatory (depolarizing) or inhibitory (hyperpolarizing) and, in some sensory neurons, their combined effects can depolarize the axon hillock enough to provoke action potentials. Examples in humans include the olfactory receptor neuron and Meissner's corpuscle, which are critical for the sense of smell and touch, respectively. However, not all sensory neurons convert their external signals into action potentials; some do not even have an axon.<sup>[38]</sup> Instead, they may convert the signal into the release of a neurotransmitter, or into continuous graded potentials, either of which may stimulate subsequent neuron(s) into firing an action potential. For illustration, in the human ear, hair cells convert the incoming sound into the opening and closing of mechanically gated ion channels, which may cause neurotransmitter molecules to be released. Similarly, in the human retina, the initial photoreceptor cells and the next two layers of cells (bipolar cells and amacrine cells) do not produce action potentials; only the third layer, the ganglion cells, produce action potentials, which then travel up the optic nerve.

## Pacemaker potentials

In the cases of neurotransmission and sensory neurons, action potentials result from an external stimulus. However, some excitable cells require no such stimulus to fire: they spontaneously depolarize their axon hillock and fire action potentials at a regular rate, like an internal clock.<sup>[39]</sup> The voltage traces of such cells are known as pacemaker potentials.<sup>[40]</sup> The cardiac pacemaker cells of the sinoatrial node in the heart provide a good example.<sup>[41]</sup> Although such pacemaker potentials have a natural rhythm, it can be adjusted by external stimuli; for instance, heart rate can be altered by pharmaceuticals as well as signals from the sympathetic and parasympathetic nerves.<sup>[42]</sup> The external stimuli do not cause the cell's repetitive firing, but merely alter its timing.<sup>[40]</sup> In some cases, the regulation of frequency can be more complex, leading to patterns of action potentials, such as bursting.



## Phases

The course of the action potential can be divided into five parts: the rising phase, the peak phase, the falling phase, the undershoot phase, and finally the refractory period. During the rising phase the membrane potential depolarizes (becomes more positive). The point at which depolarization stops is called the peak phase. At this stage, the membrane potential reaches a maximum. Subsequent to this, there is a falling phase. During this stage the membrane potential hyperpolarizes (becomes more negative). The undershoot phase is the point during which the membrane potential becomes temporarily more negatively charged than when at rest. Finally, the time during which a subsequent action potential is impossible or difficult to fire is called the refractory period, which may overlap with the other phases.<sup>[43]</sup>

The course of the action potential is determined by two coupled effects.<sup>[44]</sup> First, voltage-sensitive ion channels open and close in response to changes in the membrane voltage  $V_m$ . This changes the membrane's permeability to those ions.<sup>[45]</sup> Secondly, according to the Goldman equation, this change in permeability changes in the equilibrium potential  $E_m$ , and, thus, the membrane voltage  $V_m$ .<sup>[29]</sup> Thus, the membrane potential affects the permeability, which then further affects the membrane potential. This sets up the possibility for positive feedback, which is a key part of the rising phase of the action potential.<sup>[3]</sup> A complicating factor is that a single ion channel may have multiple internal "gates" that respond to changes in  $V_m$  in opposite ways, or at different rates.<sup>[46] [47]</sup> For example, although



raising  $V_m$  opens most gates in the voltage-sensitive sodium channel, it also closes the channel's "inactivation gate", albeit more slowly.<sup>[48]</sup> Hence, when  $V_m$  is raised suddenly, the sodium channels open initially, but then close due to the slower inactivation.

The voltages and currents of the action potential in all of its phases were modeled accurately by Alan Lloyd Hodgkin and Andrew Huxley in 1952,<sup>[47]</sup> for which they were awarded the Nobel Prize in Physiology or Medicine in 1963.<sup>[49]</sup> However, their model considers only two types of voltage-sensitive ion channels, and makes several assumptions about them, e.g., that their internal gates open and close independently of one another. In reality, there are many types of ion channels,<sup>[20]</sup> and they do not always open and close independently.<sup>[50]</sup>

## Stimulation and rising phase

A typical action potential begins at the axon hillock<sup>[51]</sup> with a sufficiently strong depolarization, e.g., a stimulus that increases  $V_m$ . This depolarization is often caused by the injection of extra sodium cations into the cell; these cations can come from a wide variety of sources, such as chemical synapses, sensory neurons or pacemaker potentials.

The initial membrane permeability to potassium is low, but much higher than that of other ions, making the resting potential close to  $E_K \approx -75$  mV.<sup>[31]</sup> The depolarization opens both the sodium and potassium channels in the membrane, allowing the ions to flow into and out of the axon, respectively. If the depolarization is small (say, increasing  $V_m$  from  $-70$  mV to  $-60$  mV), the outward potassium current overwhelms the inward sodium current and the membrane repolarizes back to its normal resting potential around  $-70$  mV.<sup>[2]</sup> However, if the depolarization is large enough, the inward sodium current increases more than the outward potassium current and a runaway condition (positive feedback) results: the more inward current there is, the more  $V_m$  increases, which in turn further increases the inward current.<sup>[3]</sup> A sufficiently strong depolarization (increase in  $V_m$ ) causes the voltage-sensitive sodium channels to open; the increasing permeability to sodium drives  $V_m$  closer to the sodium equilibrium voltage  $E_{Na} \approx +55$  mV. The increasing voltage in turn causes even more sodium channels to open, which pushes  $V_m$  still further towards  $E_{Na}$ . This positive feedback continues until the sodium channels are fully open and  $V_m$  is close to  $E_{Na}$ .<sup>[52]</sup> The sharp rise in  $V_m$  and sodium permeability correspond to the *rising phase* of the action potential.<sup>[1]</sup>

The critical threshold voltage for this runaway condition is usually around  $-45$  mV, but it depends on the recent activity of the axon. A membrane that has just fired an action potential cannot fire another one immediately, since the ion channels have not returned to their usual state. The period during which no new action potential can be fired is called the *absolute refractory period*.<sup>[53]</sup> At longer times, after some but not all of the ion channels have recovered, the axon can be stimulated to produce another action potential, but only with a much stronger depolarization, e.g.,  $-30$  mV. The period during which action potentials are unusually difficult to provoke is called the *relative refractory period*.<sup>[53]</sup>

## Peak and falling phase

The positive feedback of the rising phase slows and comes to a halt as the sodium ion channels become maximally open. At the peak of the action potential, the sodium permeability is maximized and the membrane voltage  $V_m$  is nearly equal to the sodium equilibrium voltage  $E_{Na}$ . However, the same raised voltage that opened the sodium channels initially also slowly shuts them off, by closing their pores; the sodium channels become *inactivated*.<sup>[48]</sup> This lowers the membrane's permeability to sodium, driving the membrane voltage back down. At the same time, the raised voltage opens voltage-sensitive potassium channels; the increase in the membrane's potassium permeability drives  $V_m$  towards  $E_K$ .<sup>[48]</sup> Combined, these changes in sodium and potassium permeability cause  $V_m$  to drop quickly, repolarizing the membrane and producing the "falling phase" of the action potential.<sup>[54]</sup> <sup>[54]</sup>

## Hyperpolarization ("undershoot")

The raised voltage opened many more potassium channels than usual, and these do not close right away when the membrane returns to its normal resting voltage. The potassium permeability of the membrane is transiently unusually high, driving the membrane voltage  $V_m$  even closer to the potassium equilibrium voltage  $E_K$ . Hence, there is an undershoot, a *hyperpolarization* in technical language, that persists until the membrane potassium permeability returns to its usual value.<sup>[55]</sup>

## Refractory period

Each action potential is followed by a refractory period, which can be divided into an *absolute refractory period*, during which it is impossible to evoke another action potential, and then a *relative refractory period*, during which a stronger-than-usual stimulus is required.<sup>[53]</sup> These two refractory periods are caused by changes in the state of sodium and potassium channel molecules. When closing after an action potential, sodium channels enter an "inactivated" state, in which they cannot be made to open regardless of the membrane potential—this gives rise to the absolute refractory period. Even after a sufficient number of sodium channels have transitioned back to their resting state, it frequently happens that a fraction of potassium channels remains open, making it difficult for the membrane potential to depolarize, and thereby giving rise to the relative refractory period. Because the density and subtypes of potassium channels may differ greatly between different types of neurons, the duration of the relative refractory period is highly variable.

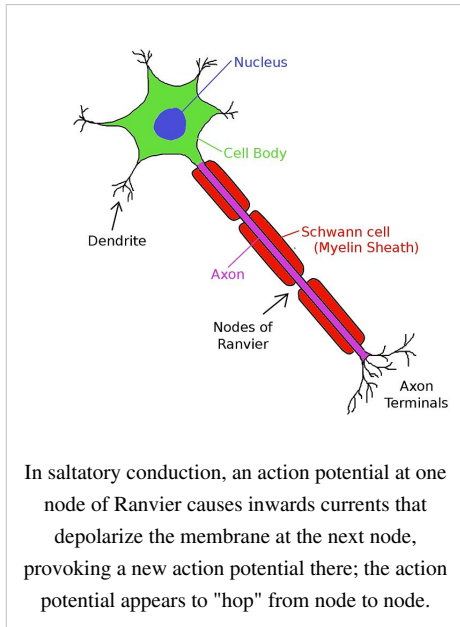
The absolute refractory period is largely responsible for the unidirectional propagation of action potentials along axons.<sup>[56]</sup> At any given moment, the patch of axon behind the actively spiking part is refractory, but the patch in front, not having been activated recently, is capable of being stimulated by the depolarization from the action potential.

## Propagation

The action potential generated at the axon hillock propagates as a wave along the axon.<sup>[57]</sup> The currents flowing inwards at a point on the axon during an action potential spread out along the axon, and depolarize the adjacent sections of its membrane. If sufficiently strong, this depolarization provokes a similar action potential at the neighboring membrane patches. This basic mechanism was demonstrated by Alan Lloyd Hodgkin in 1937. After crushing or cooling nerve segments and thus blocking the action potentials, he showed that an action potential arriving on one side of the block could provoke another action potential on the other, provided that the blocked segment was sufficiently short.<sup>[58]</sup>

Once an action potential has occurred at a patch of membrane, the membrane patch needs time to recover before it can fire again. At the molecular level, this *absolute refractory period* corresponds to the time required for the voltage-activated sodium channels to recover from inactivation, i.e. to return to their closed state.<sup>[59]</sup> There are many types of voltage-activated potassium channels in neurons, some of them inactivate fast (A-type currents) and some of them inactivate slowly or not inactivate at all; this variability guarantees that there will be always an available source of current for repolarization, even if some of the potassium channels are inactivated because of preceding depolarization. On the other hand, all neuronal voltage-activated sodium channels inactivate within several millisecond during strong depolarization, thus making following depolarization impossible until a substantial fraction of sodium channels is not returned to their closed state. Although it limits the frequency of firing,<sup>[60]</sup> the absolute refractory period ensures that the action potential moves in only one direction along an axon.<sup>[56]</sup> The currents flowing in due to an action potential spread out in both directions along the axon.<sup>[61]</sup> However, only the unfired part of the axon can respond with an action potential; the part that has just fired is unresponsive until the action potential is safely out of range and cannot restimulate that part. In the usual orthodromic conduction, the action potential propagates from the axon hillock towards the synaptic knobs (the axonal termini); propagation in the opposite direction—known as antidromic conduction—is very rare.<sup>[62]</sup> However, if a laboratory axon is stimulated in

its middle, both halves of the axon are "fresh", i.e., unfired; then two action potentials will be generated, one traveling towards the axon hillock and the other traveling towards the synaptic knobs.



### Myelin and saltatory conduction

The evolutionary need for the fast and efficient transduction of electrical signals in nervous system resulted in appearance of myelin sheaths around neuronal axons. Myelin is a multilamellar membrane which enwraps the axon in segments separated by intervals known as nodes of Ranvier, is produced by specialized cells, Schwann cells exclusively in the peripheral nervous system, and by oligodendrocytes exclusively in the central nervous system. Myelin sheath reduces membrane capacitance and increases membrane resistance in the inter-node intervals, thus allowing a fast, saltatory movement of action potentials from node to node.<sup>[63] [64] [65]</sup> Myelination is found mainly in vertebrates, but an analogous system has been discovered in a few invertebrates, such as some species of shrimp.<sup>[66]</sup> Not all neurons in vertebrates are myelinated; for example, axons of the neurons comprising autonomous (vegetative) nervous system are not myelinated in general.

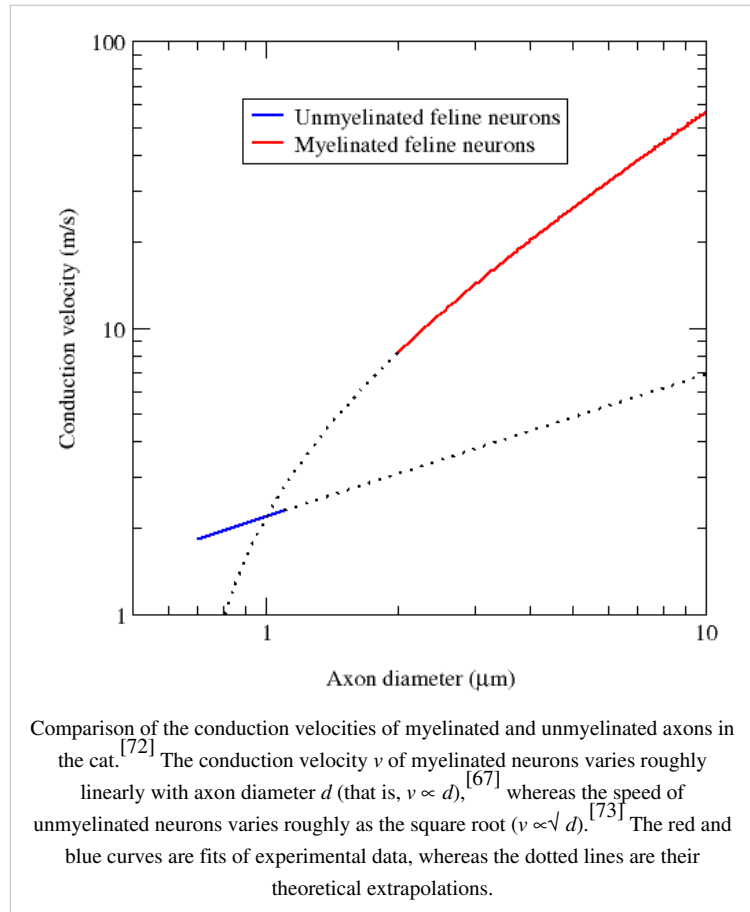
Myelin prevents ions from entering or leaving the axon along myelinated segments. As a general rule, myelination increases the conduction velocity of action potentials and makes them more energy-efficient. Whether saltatory or not, the mean conduction velocity of an action potential ranges from 1 m/s to over 100 m/s, and generally increases with axonal diameter.<sup>[67]</sup>

Action potentials cannot propagate through the membrane in myelinated segments of the axon. However, the current is carried by the cytoplasm, which is sufficient to depolarize the next 1 or 2 node of Ranvier. Instead, the ionic current from an action potential at one node of Ranvier provokes another action potential at the next node; this apparent "hopping" of the action potential from node to node is known as saltatory conduction. Although the mechanism of saltatory conduction was suggested in 1925 by Ralph Lillie,<sup>[68]</sup> the first experimental evidence for saltatory conduction came from Ichiji Tasaki<sup>[69]</sup> and Taiji Takeuchi<sup>[70]</sup> and from Andrew Huxley and Robert Stämpfli.<sup>[71]</sup> By contrast, in unmyelinated axons, the action potential provokes another in the membrane immediately adjacent, and moves continuously down the axon like a wave.

Myelin has two important advantages: fast conduction speed and energy efficiency. For axons larger than a minimum diameter (roughly 1 micrometre), myelination increases the conduction velocity of an action potential, typically tenfold.<sup>[74]</sup> Conversely, for a given conduction velocity, myelinated fibers are smaller than their unmyelinated counterparts. For example, action potentials move at roughly the same speed (25 m/s) in a myelinated frog axon and an unmyelinated squid giant axon, but the frog axon has a roughly 30-fold smaller diameter and 1000-fold smaller cross-sectional area. Also, since the ionic currents are confined to the nodes of Ranvier, far fewer ions "leak" across the membrane, saving metabolic energy. This saving is a significant selective advantage, since the human nervous system uses approximately 20% of the body's metabolic energy.<sup>[74]</sup>

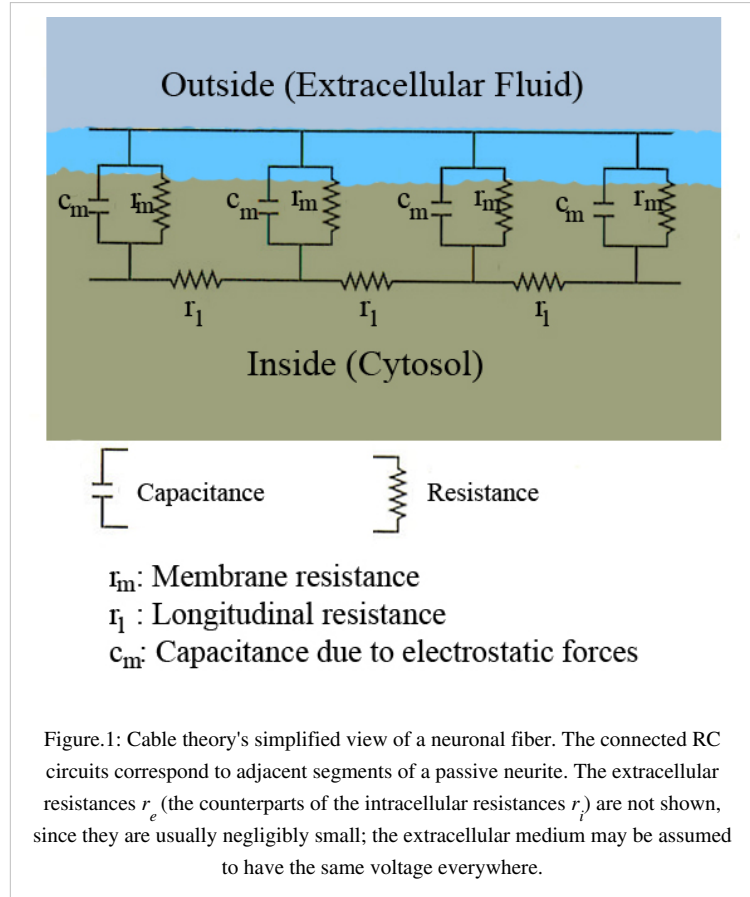
The length of axons' myelinated segments is important to the success of saltatory conduction. They should be as long as possible to maximize the speed of conduction, but not so long that the arriving signal is too weak to provoke an action potential at the next node of Ranvier. In nature, myelinated segments are generally long enough for the passively propagated signal to travel for at least two nodes while retaining enough amplitude to fire an action potential at the second or third node. Thus, the safety factor of saltatory conduction is high, allowing transmission to bypass nodes in case of injury. However, action potentials may end prematurely in certain places where the safety factor is low, even in unmyelinated neurons; a common example is the branch point of an axon, where it divides into two axons.<sup>[75]</sup>

Some diseases degrade myelin and impair saltatory conduction, reducing the conduction velocity of action potentials.<sup>[76]</sup> The most well-known of these is multiple sclerosis, in which the breakdown of myelin impairs coordinated movement.<sup>[77]</sup>



## Cable theory

The flow of currents within an axon can be described quantitatively by cable theory<sup>[78]</sup> and its elaborations, such as the compartmental model.<sup>[79]</sup> Cable theory was developed in 1855 by Lord Kelvin to model the transatlantic telegraph cable<sup>[80]</sup> and was shown to be relevant to neurons by Hodgkin and Rushton in 1946.<sup>[81]</sup> In simple cable theory, the neuron is treated as an electrically passive, perfectly cylindrical transmission cable, which can be described by a partial differential equation<sup>[78]</sup>



$$\tau \frac{\partial V}{\partial t} = \lambda^2 \frac{\partial^2 V}{\partial x^2} - V$$

where  $V(x, t)$  is the voltage across the membrane at a time  $t$  and a position  $x$  along the length of the neuron, and where  $\lambda$  and  $\tau$  are the characteristic length and time scales on which those voltages decay in response to a stimulus. Referring to the circuit diagram above, these scales can be determined from the resistances and capacitances per unit length<sup>[82]</sup>

$$\tau = r_m c_m$$

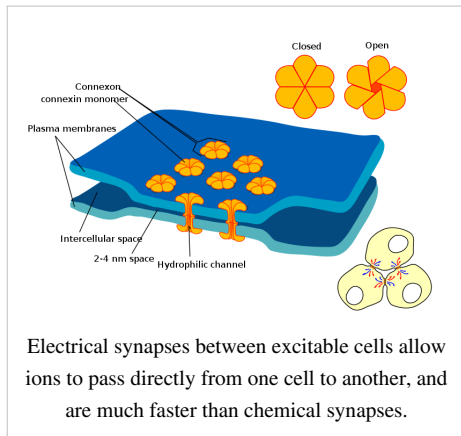
$$\lambda = \sqrt{\frac{r_m}{r_l}}$$

These time- and length-scales can be used to understand the dependence of the conduction velocity on the diameter of the neuron in unmyelinated fibers. For example, the time-scale  $\tau$  increases with both the membrane resistance  $r_m$  and capacitance  $c_m$ . As the capacitance increases, more charge must be transferred to produce a given transmembrane voltage (by the equation  $Q=CV$ ); as the resistance increases, less charge is transferred per unit time, making the equilibration slower. Similarly, if the internal resistance per unit length  $r_l$  is lower in one axon than in another (e.g., because the radius of the former is larger), the spatial decay length  $\lambda$  becomes longer and the conduction velocity of an action potential should increase. If the transmembrane resistance  $r_m$  is increased, that lowers the average "leakage" current across the membrane, likewise causing  $\lambda$  to become longer, increasing the conduction velocity.

## Termination

### Chemical synapses

Action potentials that reach the synaptic knobs generally cause a neurotransmitter to be released into the synaptic cleft.<sup>[83]</sup> Neurotransmitters are small molecules that may open ion channels in the postsynaptic cell; most axons have the same neurotransmitter at all of their termini. The arrival of the action potential opens voltage-sensitive calcium channels in the presynaptic membrane; the influx of calcium causes vesicles filled with neurotransmitter to migrate to the cell's surface and release their contents into the synaptic cleft.<sup>[84]</sup> This complex process is inhibited by the neurotoxins tetanospasmin and botulinum toxin, which are responsible for tetanus and botulism, respectively.<sup>[85]</sup>



### Electrical synapses

Some synapses dispense with the "middleman" of the neurotransmitter, and connect the presynaptic and postsynaptic cells together.<sup>[86]</sup> When an action potential reaches such a synapse, the ionic currents flowing into the presynaptic cell can cross the barrier of the two cell membranes and enter the postsynaptic cell through pores known as connexins.<sup>[87]</sup> Thus, the ionic currents of the presynaptic action potential can directly stimulate the postsynaptic cell. Electrical synapses allow for faster transmission because they do not require the slow diffusion of neurotransmitters across the synaptic cleft. Hence, electrical synapses are used whenever fast response and coordination

of timing are crucial, as in escape reflexes, the retina of vertebrates, and the heart.

### Neuromuscular junctions

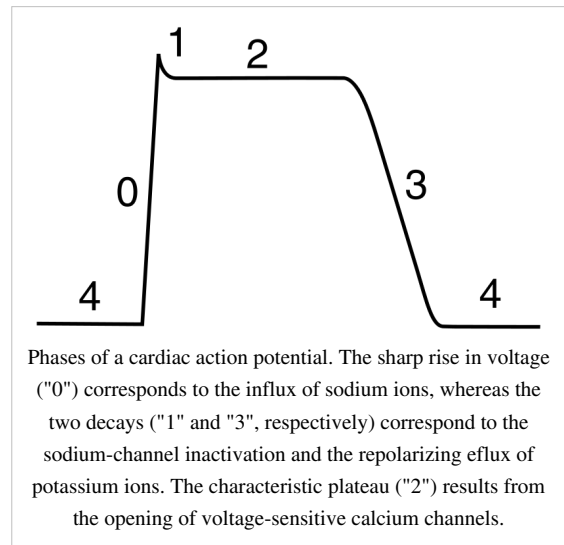
A special case of a chemical synapse is the neuromuscular junction, in which the axon of a motor neuron terminates on a muscle fiber.<sup>[88]</sup> In such cases, the released neurotransmitter is acetylcholine, which binds to the acetylcholine receptor, an integral membrane protein in the membrane (the *sarcolemma*) of the muscle fiber.<sup>[89]</sup> However, the acetylcholine does not remain bound; rather, it dissociates and is hydrolyzed by the enzyme, acetylcholinesterase, located in the synapse. This enzyme quickly reduces the stimulus to the muscle, which allows the degree and timing of muscular contraction to be regulated delicately. Some poisons inactivate acetylcholinesterase to prevent this control, such as the nerve agents sarin and tabun,<sup>[90]</sup> and the insecticides diazinon and malathion.<sup>[91]</sup>

## Other cell types

### Cardiac action potentials

The cardiac action potential differs from the neuronal action potential by having an extended plateau, in which the membrane is held at a high voltage for a few hundred milliseconds prior to being repolarized by the potassium current as usual.<sup>[92]</sup> This plateau is due to the action of slower calcium channels opening and holding the membrane voltage near their equilibrium potential even after the sodium channels have inactivated.

The cardiac action potential plays an important role in coordinating the contraction of the heart.<sup>[92]</sup> The cardiac cells of the sinoatrial node provide the pacemaker potential that synchronizes the heart. The action potentials of those cells propagate to and through the atrioventricular node (AV node), which is normally the only conduction pathway between the atria and the ventricles. Action potentials from the AV node travel through the bundle of His and thence to the Purkinje fibers.<sup>[93]</sup> Conversely, anomalies in the cardiac action potential—whether due to a congenital mutation or injury—can lead to human pathologies, especially arrhythmias.<sup>[92]</sup> Several anti-arrhythmia drugs act on the cardiac action potential, such as quinidine, lidocaine, beta blockers, and verapamil.<sup>[94]</sup>



### Muscular action potentials

The action potential in a normal skeletal muscle cell is similar to the action potential in neurons.<sup>[95]</sup> Action potentials result from the depolarization of the cell membrane (the sarcolemma), which opens voltage-sensitive sodium channels; these become inactivated and the membrane is repolarized through the outward current of potassium ions. The resting potential prior to the action potential is typically  $-90\text{mV}$ , somewhat more negative than typical neurons. The muscle action potential lasts roughly 2–4 ms, the absolute refractory period is roughly 1–3 ms, and the conduction velocity along the muscle is roughly 5 m/s. The action potential releases calcium ions that free up the tropomyosin and allow the muscle to contract. Muscle action potentials are provoked by the arrival of a pre-synaptic neuronal action potential at the neuromuscular junction, which is a common target for neurotoxins.<sup>[90]</sup>

### Plant action potentials

Plant and fungal cells<sup>[96]</sup> are also electrically excitable. The fundamental difference to animal action potentials is, that the depolarization in plant cells is not accomplished by an uptake of positive sodium ions, but by release of negative *chloride* ions.<sup>[97] [98] [99]</sup> Together with the following release of positive potassium ions, which is common to plant and animal action potentials, the action potential in plants infers, therefore, an osmotic loss of salt (KCl), whereas the animal action potential is osmotically neutral, when equal amounts of entering sodium and leaving potassium cancel each other osmotically. The interaction of electrical and osmotic relations in plant cells<sup>[100]</sup> indicates an osmotic function of electrical excitability in the common, unicellular ancestors of plants and animals under changing salinity conditions, whereas the present function of rapid signal transmission is seen as a younger accomplishment of metazoan cells in a more stable osmotic environment<sup>[101]</sup>. It must be assumed that the familiar signalling function of action potentials in some vascular plants (e.g. *Mimosa pudica*), arose independently from that in metazoan excitable cells.

Taxonomic distribution and evolutionary advantages

Action potentials are found throughout multicellular organisms, including plants, invertebrates such as insects, and vertebrates such as reptiles and mammals.<sup>[102]</sup> Sponges seem to be the main phylum of multicellular eukaryotes that does not transmit action potentials, although some studies have suggested that these organisms have a form of electrical signaling, too.<sup>[103]</sup> The resting potential, as well as the size and duration of the action potential, have not varied much with evolution, although the conduction velocity does vary dramatically with axonal diameter and myelination.

Comparison of action potentials (APs) from a representative cross-section of animals<sup>[104]</sup>

| Animal                           | Cell type           | Resting potential (mV) | AP increase (mV) | AP duration (ms) | Conduction speed (m/s) |
|----------------------------------|---------------------|------------------------|------------------|------------------|------------------------|
| Squid ( <i>Loligo</i> )          | Giant axon          | −60                    | 120              | 0.75             | 35                     |
| Earthworm ( <i>Lumbricus</i> )   | Median giant fiber  | −70                    | 100              | 1.0              | 30                     |
| Cockroach ( <i>Periplaneta</i> ) | Giant fiber         | −70                    | 80–104           | 0.4              | 10                     |
| Frog ( <i>Rana</i> )             | Sciatic nerve axon  | −60 to −80             | 110–130          | 1.0              | 7–30                   |
| Cat ( <i>Felis</i> )             | Spinal motor neuron | −55 to −80             | 80–110           | 1–1.5            | 30–120                 |

Given its conservation throughout evolution, the action potential seems to confer evolutionary advantages. One function of action potentials is rapid, long-range signaling within the organism; the conduction velocity can exceed 110 m/s, which is one-third the speed of sound. No material object could convey a signal that rapidly throughout the body; for comparison, a hormone molecule carried in the bloodstream moves at roughly 8 m/s in large arteries. Part of this function is the tight coordination of mechanical events, such as the contraction of the heart. A second function is the computation associated with its generation. Being an all-or-none signal that does not decay with transmission distance, the action potential has similar advantages to digital electronics. The integration of various dendritic signals at the axon hillock and its thresholding to form a complex train of action potentials is another form of computation, one that has been exploited biologically to form central pattern generators and mimicked in artificial neural networks.

Experimental methods

The study of action potentials has required the development of new experimental methods. The initial work, prior to 1955, focused on three goals: isolating signals from single neurons or axons, developing fast, sensitive electronics, and shrinking electrodes enough that the voltage inside a single cell could be recorded.

The first problem was solved by studying the giant axons found in the neurons of the squid genus *Loligo*.<sup>[105]</sup> These axons are so large in diameter (roughly 1 mm, or 100-fold larger than a typical neuron) that they can be seen with the naked eye, making them easy to extract and manipulate.<sup>[47]</sup> <sup>[106]</sup> However, the *Loligo* axons are not representative of all excitable cells, and numerous other systems with action potentials have been studied.

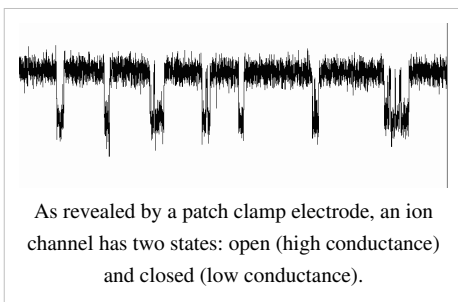


The giant axons of the European squid (*Loligo vulgaris*) were crucial for scientists to understand the action potential.



The second problem was addressed with the crucial development of the voltage clamp,<sup>[107]</sup> which permitted experimenters to study the ionic currents underlying an action potential in isolation, and eliminated a key source of electronic noise, the current  $I_C$  associated with the capacitance  $C$  of the membrane.<sup>[108]</sup> Since the current equals  $C$  times the rate of change of the transmembrane voltage  $V_m$ , the solution was to design a circuit that kept  $V_m$  fixed (zero rate of change) regardless of the currents flowing across the membrane. Thus, the current required to keep  $V_m$  at a fixed value is a direct reflection of the current flowing through the membrane. Other electronic advances included the use of Faraday cages and electronics with high input impedance, so that the measurement itself did not affect the voltage being measured.<sup>[109]</sup>

The third problem, that of obtaining electrodes small enough to record voltages within a single axon without perturbing it, was solved in 1949 with the invention of the glass micropipette electrode,<sup>[110]</sup> which was quickly adopted by other researchers.<sup>[111] [112]</sup> Refinements of this method are able to produce electrode tips that are as fine as 100 Å (10 nm), which also confers high input impedance.<sup>[113]</sup> Action potentials may also be recorded with small metal electrodes placed just next to a neuron, with neurochips containing EOSFETs, or optically with dyes that are sensitive to  $\text{Ca}^{2+}$  or to voltage.<sup>[114]</sup>

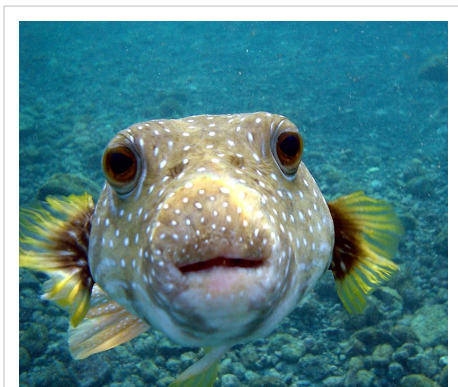


While glass micropipette electrodes measure the sum of the currents passing through many ion channels, studying the electrical properties of a single ion channel became possible in the 1970s with the development of the patch clamp by Erwin Neher and Bert Sakmann. For this they were awarded the Nobel Prize in Physiology or Medicine in 1991.<sup>[115]</sup> Patch-clamping verified that ionic channels have discrete states of conductance, such as open, closed and inactivated.

Optical imaging technologies have been developed in recent years to measure action potentials, either via simultaneous multisite recordings or with ultra spatial resolution. Using voltage-sensitive dyes, action potentials have been optically recorded from a tiny patch of cardiomyocyte membrane.<sup>[116]</sup>

## Neurotoxins

Several neurotoxins, both natural and synthetic, are designed to block the action potential. Tetrodotoxin from the pufferfish and saxitoxin from the *Gonyaulax* (the dinoflagellate genus responsible for "red tides") block action potentials by inhibiting the voltage-sensitive sodium channel;<sup>[117]</sup> similarly, dendrotoxin from the black mamba snake inhibits the voltage-sensitive potassium channel. Such inhibitors of ion channels serve an important research purpose, by allowing scientists to "turn off" specific channels at will, thus isolating the other channels' contributions; they can also be useful in purifying ion channels by affinity chromatography or in assaying their concentration. However, such inhibitors also make effective neurotoxins, and have been considered for use as chemical weapons. Neurotoxins aimed at the ion channels of insects have been effective insecticides; one example is the synthetic permethrin, which prolongs the activation of the sodium channels involved in action potentials. The ion channels of insects are sufficiently different from their human counterparts that there are few side effects in humans. Many other neurotoxins interfere with the transmission of the action potential's effects at the synapses, especially at the neuromuscular junction.



Tetrodotoxin is a lethal toxin from the pufferfish that inhibits the voltage-sensitive sodium channel, halting action potentials.

## History

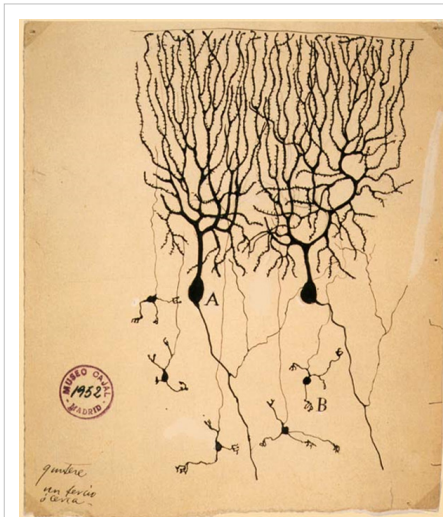


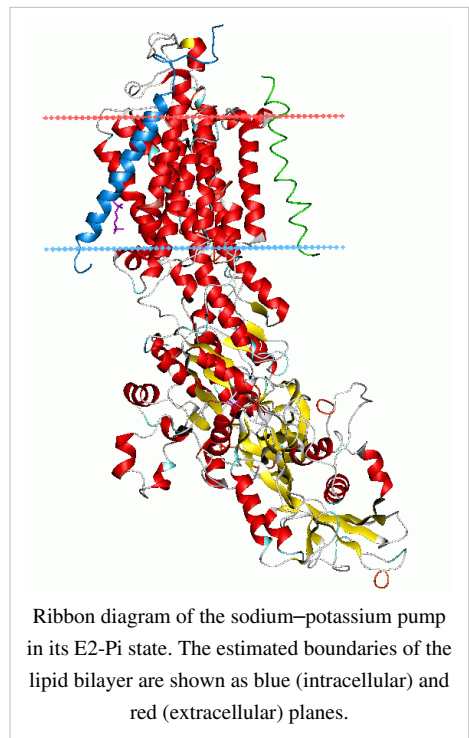
Image of two Purkinje cells (labeled as **A**) drawn by Santiago Ramón y Cajal. Large trees of dendrites feed into the soma, from which a single axon emerges and moves generally downwards with a few branch points. The smaller cells labeled **B** are granule cells.

The role of electricity in the nervous systems of animals was first observed in dissected frogs by Luigi Galvani, who studied it from 1791 to 1797.<sup>[118]</sup> Galvani's results stimulated Alessandro Volta to develop the Voltaic pile—the earliest known electric battery—with which he studied animal electricity (such as electric eels) and the physiological responses to applied direct-current voltages.<sup>[119]</sup>

Scientists of the 19th century studied the propagation of electrical signals in whole nerves (i.e., bundles of neurons) and demonstrated that nervous tissue was made up of cells, instead of an interconnected network of tubes (a *reticulum*).<sup>[120]</sup> Carlo Matteucci followed up Galvani's studies and demonstrated that cell membranes had a voltage across them and could produce direct current. Matteucci's work inspired the German physiologist, Emil du Bois-Reymond, who discovered the action potential in 1848. The conduction velocity of action potentials was first measured in 1850 by du Bois-Reymond's friend, Hermann von Helmholtz. To establish that nervous tissue was made up of discrete cells, the Spanish physician Santiago Ramón y Cajal and his students used a stain developed by Camillo Golgi to reveal the myriad shapes of neurons, which they rendered

painstakingly. For their discoveries, Golgi and Ramón y Cajal were awarded the 1906 Nobel Prize in Physiology.<sup>[121]</sup> Their work resolved a long-standing controversy in the neuroanatomy of the 19th century; Golgi himself had argued for the network model of the nervous system.

The 20th century was a golden era for electrophysiology. In 1902 and again in 1912, Julius Bernstein advanced the hypothesis that the action potential resulted from a change in the permeability of the axonal membrane to ions.<sup>[126]</sup> Bernstein's hypothesis was confirmed by Ken Cole and Howard Curtis, who showed that membrane conductance increases during an action potential.<sup>[122]</sup> In 1907, Louis Lapicque suggested that the action potential was generated as a threshold was crossed<sup>[123]</sup>, what would be later shown as a product of the dynamical systems of ionic conductances. In 1949, Alan Hodgkin and Bernard Katz refined Bernstein's hypothesis by considering that the axonal membrane might have different permeabilities to different ions; in particular, they demonstrated the crucial role of the sodium permeability for the action potential.<sup>[32]</sup> This line of research culminated in the five 1952 papers of Hodgkin, Katz and Andrew Huxley, in which they applied the voltage clamp technique to determine the dependence of the axonal membrane's permeabilities to sodium and potassium ions on voltage and time, from which they were able to reconstruct the action potential quantitatively.<sup>[47]</sup> Hodgkin and Huxley correlated the properties of their mathematical model with discrete ion channels that could exist in several different states, including "open", "closed", and "inactivated". Their hypotheses were confirmed in the mid-1970s and 1980s by Erwin Neher and Bert Sakmann, who developed the

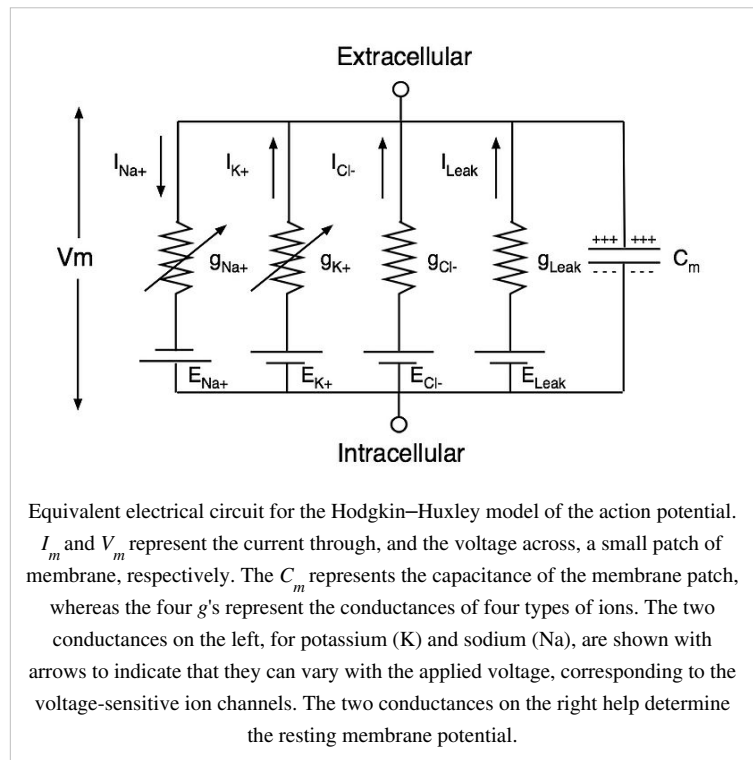


technique of patch clamping to examine the conductance states of individual ion channels.<sup>[124]</sup> In the 21st century, researchers are beginning to understand the structural basis for these conductance states and for the selectivity of channels for their species of ion,<sup>[125]</sup> through the atomic-resolution crystal structures,<sup>[15]</sup> fluorescence distance measurements<sup>[126]</sup> and cryo-electron microscopy studies.<sup>[127]</sup>

Julius Bernstein was also the first to introduce the Nernst equation for resting potential across the membrane; this was generalized by David E. Goldman to the eponymous Goldman equation in 1943.<sup>[29]</sup> The sodium–potassium pump was identified in 1957<sup>[128]</sup> and its properties gradually elucidated,<sup>[21] [22] [129]</sup> culminating in the determination of its atomic-resolution structure by X-ray crystallography.<sup>[130]</sup> The crystal structures of related ionic pumps have also been solved, giving a broader view of how these molecular machines work.<sup>[131]</sup>

## Quantitative models

Mathematical and computational models are essential for understanding the action potential, and offer predictions that may be tested against experimental data, providing a stringent test of a theory. The most important and accurate of these models is the Hodgkin–Huxley model, which describes the action potential by a coupled set of four ordinary differential equations (ODEs).<sup>[47]</sup> Although the Hodgkin–Huxley model may be a simplification of a realistic nervous membrane as it exists in nature, its complexity has inspired several even-more-simplified models,<sup>[132]</sup> such as the Morris–Lecar model<sup>[133]</sup> and the FitzHugh–Nagumo model,<sup>[134]</sup> both of which have only two coupled ODEs. The properties of the Hodgkin–Huxley and FitzHugh–Nagumo models and their relatives, such as the Bonhoeffer–van der Pol model,<sup>[135]</sup> have been well-studied within mathematics,<sup>[136]</sup> computation<sup>[137]</sup> and electronics.<sup>[138]</sup> More modern research has focused on larger and more integrated systems; by joining action-potential models with models of other parts of the nervous system (such as dendrites and synapses), researches can study neural computation<sup>[139]</sup> and simple reflexes, such as escape reflexes and others controlled by central pattern generators.<sup>[140]</sup>



## See also

- Bursting
- Signals (biology)
- Central pattern generator

## Notes

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## External links

### Animations

- Ionic flow in action potentials (<http://www.blackwellpublishing.com/matthews/channel.html>) at Blackwell Publishing
- Action potential propagation in myelinated and unmyelinated axons (<http://www.blackwellpublishing.com/matthews/actionp.html>) at Blackwell Publishing
- Generation of AP in cardiac cells (<http://thevirtualheart.org/CAPindex.html>) and generation of AP in neuron cells (<http://thevirtualheart.org/java/neuron/apneuron.html>)
- Resting membrane potential (<http://bcs.whfreeman.com/thelifewire/content/chp44/4402001.html>) from *Life: The Science of Biology*, by WK Purves, D Sadava, GH Orians, and HC Heller, 8th edition, New York: WH Freeman, ISBN 978-0716776710.
- Ionic motion and the Goldman voltage for arbitrary ionic concentrations (<http://www.nernstgoldman.physiology.arizona.edu/>) at The University of Arizona
- A cartoon illustrating the action potential ([http://www.brainu.org/files/movies/action\\_potential\\_cartoon.swf](http://www.brainu.org/files/movies/action_potential_cartoon.swf))
- Action potential Propagation (<http://www.1lecture.com/Biochemistry/Action Potential/index.html>)

### Lecture notes and other materials

- The Action Potential (<http://www.du.edu/~kinnamon/3640/actionpotential/ap1.html>) John Kinnamon, University of Denver
- Resting and Action Membrane Potentials (<http://trc.ucdavis.edu/biosci10v/bis10v/week10/06potential.html>) Teaching Resources Center, UC Davis. Animated tutorials
- Open-source software to simulate neuronal and cardiac action potentials (<http://cese.sourceforge.net/>) at SourceForge.net

## Mathematical logic

**Mathematical logic** is a subfield of mathematics with close connections to computer science and philosophical logic.<sup>[1]</sup> The field includes both the mathematical study of logic and the applications of formal logic to other areas of mathematics. The unifying themes in mathematical logic include the study of the expressive power of formal systems and the deductive power of formal proof systems.

Mathematical logic is often divided into the fields of set theory, model theory, recursion theory, and proof theory. These areas share basic results on logic, particularly first-order logic, and definability. In computer science (particularly in the ACM Classification) mathematical logic is seen as encompassing additional topics that are not detailed in this article; see logic in computer science for those.

Since its inception, mathematical logic has contributed to, and has been motivated by, the study of foundations of mathematics. This study began in the late 19th century with the development of axiomatic frameworks for geometry, arithmetic, and analysis. In the early 20th century it was shaped by David Hilbert's program to prove the consistency of foundational theories. Results of Kurt Gödel, Gerhard Gentzen, and others provided partial resolution to the program, and clarified the issues involved in proving consistency. Work in set theory showed that almost all ordinary mathematics can be formalized in terms of sets, although there are some theorems that cannot be proven in common axiom systems for set theory. Contemporary work in the foundations of mathematics often focuses on establishing which parts of mathematics can be formalized in particular formal systems, rather than trying to find theories in which all of mathematics can be developed.

## History

Mathematical logic emerged in the mid-19th century as a subfield of mathematics independent of the traditional study of logic (Ferreirós 2001, p. 443). Before this emergence, logic was studied with rhetoric, through the syllogism, and with philosophy. The first half of the 20th century saw an explosion of fundamental results, accompanied by vigorous debate over the foundations of mathematics.

### Early history

Sophisticated theories of logic were developed in many cultures, including China, India, Greece and the Islamic world. In the 18th century, attempts to treat the operations of formal logic in a symbolic or algebraic way had been made by philosophical mathematicians including Leibniz and Lambert, but their labors remained isolated and little known.

### 19th century

In the middle of the nineteenth century, George Boole and then Augustus De Morgan presented systematic mathematical treatments of logic. Their work, building on work by algebraists such as George Peacock, extended the traditional Aristotelian doctrine of logic into a sufficient framework for the study of foundations of mathematics (Katz 1998, p. 686).

Charles Sanders Peirce built upon the work of Boole to develop a logical system for relations and quantifiers, which he published in several papers from 1870 to 1885. Gottlob Frege presented an independent development of logic with quantifiers in his *Begriffsschrift*, published in 1879. Frege's work remained obscure, however, until Bertrand Russell began to promote it near the turn of the century. The two-dimensional notation Frege developed was never widely adopted and is unused in contemporary texts.

From 1890 to 1905, Ernst Schröder published *Vorlesungen über die Algebra der Logik* in three volumes. This work summarized and extended the work of Boole, De Morgan, and Peirce, and was a comprehensive reference to symbolic logic as it was understood at the end of the 19th century.

### Foundational theories

Some concerns that mathematics had not been built on a proper foundation led to the development of axiomatic systems for fundamental areas of mathematics such as arithmetic, analysis, and geometry.

In logic, the term *arithmetic* refers to the theory of the natural numbers. Giuseppe Peano (1888) published a set of axioms for arithmetic that came to bear his name (Peano axioms), using a variation of the logical system of Boole and Schröder but adding quantifiers. Peano was unaware of Frege's work at the time. Around the same time Richard Dedekind showed that the natural numbers are uniquely characterized by their induction properties. Dedekind (1888) proposed a different characterization, which lacked the formal logical character of Peano's axioms. Dedekind's work, however, proved theorems inaccessible in Peano's system, including the uniqueness of the set of natural numbers (up to isomorphism) and the recursive definitions of addition and multiplication from the successor function and mathematical induction.

In the mid-19th century, flaws in Euclid's axioms for geometry became known (Katz 1998, p. 774). In addition to the independence of the parallel postulate, established by Nikolai Lobachevsky in 1826 (Lobachevsky 1840), mathematicians discovered that certain theorems taken for granted by Euclid were not in fact provable from his axioms. Among these is the theorem that a line contains at least two points, or that circles of the same radius whose centers are separated by that radius must intersect. Hilbert (1899) developed a complete set of axioms for geometry, building on previous work by Pasch (1882). The success in axiomatizing geometry motivated Hilbert to seek complete axiomatizations of other areas of mathematics, such as the natural numbers and the real line. This would prove to be a major area of research in the first half of the 20th century.

The 19th century saw great advances in the theory of real analysis, including theories of convergence of functions and Fourier series. Mathematicians such as Karl Weierstrass began to construct functions that stretched intuition, such as nowhere-differentiable continuous functions. Previous conceptions of a function as a rule for computation, or a smooth graph, were no longer adequate. Weierstrass began to advocate the arithmetization of analysis, which sought to axiomatize analysis using properties of the natural numbers. The modern  $(\epsilon, \delta)$ -definition of limit and continuous functions was already developed by Bolzano in 1817 (Felscher 2000), but remained relatively unknown. Cauchy in 1821 defined continuity in terms of infinitesimals (see *Cours d'Analyse*, page 34). In 1858, Dedekind proposed a definition of the real numbers in terms of Dedekind cuts of rational numbers (Dedekind 1872), a definition still employed in contemporary texts.

Georg Cantor developed the fundamental concepts of infinite set theory. His early results developed the theory of cardinality and proved that the reals and the natural numbers have different cardinalities (Cantor 1874). Over the next twenty years, Cantor developed a theory of transfinite numbers in a series of publications. In 1891, he published a new proof of the uncountability of the real numbers that introduced the diagonal argument, and used this method to prove Cantor's theorem that no set can have the same cardinality as its powerset. Cantor believed that every set could be well-ordered, but was unable to produce a proof for this result, leaving it as an open problem in 1895 (Katz 1998, p. 807).

## 20th century

In the early decades of the 20th century, the main areas of study were set theory and formal logic. The discovery of paradoxes in informal set theory caused some to wonder whether mathematics itself is inconsistent, and to look for proofs of consistency.

In 1900, Hilbert posed a famous list of 23 problems for the next century. The first two of these were to resolve the continuum hypothesis and prove the consistency of elementary arithmetic, respectively; the tenth was to produce a method that could decide whether a multivariate polynomial equation over the integers has a solution. Subsequent work to resolve these problems shaped the direction of mathematical logic, as did the effort to resolve Hilbert's *Entscheidungsproblem*, posed in 1928. This problem asked for a procedure that would decide, given a formalized mathematical statement, whether the statement is true or false.

### Set theory and paradoxes

Ernst Zermelo (1904) gave a proof that every set could be well-ordered, a result Georg Cantor had been unable to obtain. To achieve the proof, Zermelo introduced the axiom of choice, which drew heated debate and research among mathematicians and the pioneers of set theory. The immediate criticism of the method led Zermelo to publish a second exposition of his result, directly addressing criticisms of his proof (Zermelo 1908). This paper led to the general acceptance of the axiom of choice in the mathematics community.

Skepticism about the axiom of choice was reinforced by recently discovered paradoxes in naive set theory. Cesare Burali-Forti (1897) was the first to state a paradox: the Burali-Forti paradox shows that the collection of all ordinal numbers cannot form a set. Very soon thereafter, Bertrand Russell discovered Russell's paradox in 1901, and Jules Richard (1905) discovered Richard's paradox.

Zermelo (1908) provided the first set of axioms for set theory. These axioms, together with the additional axiom of replacement proposed by Abraham Fraenkel, are now called Zermelo–Fraenkel set theory (ZF). Zermelo's axioms incorporated the principle of limitation of size to avoid Russell's paradox.

In 1910, the first volume of *Principia Mathematica* by Russell and Alfred North Whitehead was published. This seminal work developed the theory of functions and cardinality in a completely formal framework of type theory, which Russell and Whitehead developed in an effort to avoid the paradoxes. *Principia Mathematica* is considered one of the most influential works of the 20th century, although the framework of type theory did not prove popular as a foundational theory for mathematics (Ferreirós 2001, p. 445).

Fraenkel (1922) proved that the axiom of choice cannot be proved from the remaining axioms of Zermelo's set theory with urelements. Later work by Paul Cohen (1966) showed that the addition of urelements is not needed, and the axiom of choice is unprovable in ZF. Cohen's proof developed the method of forcing, which is now an important tool for establishing independence results in set theory.

### Symbolic logic

Leopold Löwenheim (1918) and Thoralf Skolem (1919) obtained the Löwenheim–Skolem theorem, which says that first-order logic cannot control the cardinalities of infinite structures. Skolem realized that this theorem would apply to first-order formalizations of set theory, and that it implies any such formalization has a countable model. This counterintuitive fact became known as Skolem's paradox.

In his doctoral thesis, Kurt Gödel (1929) proved the completeness theorem, which establishes a correspondence between syntax and semantics in first-order logic. Gödel used the completeness theorem to prove the compactness theorem, demonstrating the finitary nature of first-order logical consequence. These results helped establish first-order logic as the dominant logic used by mathematicians.

In 1931, Gödel published *On Formally Undecidable Propositions of Principia Mathematica and Related Systems*, which proved the incompleteness (in a different meaning of the word) of all sufficiently strong, effective first-order theories. This result, known as Gödel's incompleteness theorem, establishes severe limitations on axiomatic foundations for mathematics, striking a strong blow to Hilbert's program. It showed the impossibility of providing a consistency proof of arithmetic within any formal theory of arithmetic. Hilbert, however, did not acknowledge the importance of the incompleteness theorem for some time.

Gödel's theorem shows that a consistency proof of any sufficiently strong, effective axiom system cannot be obtained in the system itself, if the system is consistent, nor in any weaker system. This leaves open the possibility of consistency proofs that cannot be formalized within the system they consider. Gentzen (1936) proved the consistency of arithmetic using a finitistic system together with a principle of transfinite induction. Gentzen's result introduced the ideas of cut elimination and proof-theoretic ordinals, which became key tools in proof theory. Gödel (1958) gave a different consistency proof, which reduces the consistency of classical arithmetic to that of intuitionistic arithmetic in higher types.

### Beginnings of the other branches

Alfred Tarski developed the basics of model theory.

Beginning in 1935, a group of prominent mathematicians collaborated under the pseudonym Nicolas Bourbaki to publish a series of encyclopedic mathematics texts. These texts, written in an austere and axiomatic style, emphasized rigorous presentation and set-theoretic foundations. Terminology coined by these texts, such as the words *bijection*, *injection*, and *surjection*, and the set-theoretic foundations the texts employed, were widely adopted throughout mathematics.

The study of computability came to be known as recursion theory, because early formalizations by Gödel and Kleene relied on recursive definitions of functions.<sup>[2]</sup> When these definitions were shown equivalent to Turing's formalization involving Turing machines, it became clear that a new concept – the computable function – had been discovered, and that this definition was robust enough to admit numerous independent characterizations. In his work on the incompleteness theorems in 1931, Gödel lacked a rigorous concept of an effective formal system; he immediately realized that the new definitions of computability could be used for this purpose, allowing him to state the incompleteness theorems in generality that could only be implied in the original paper.

Numerous results in recursion theory were obtained in the 1940s by Stephen Cole Kleene and Emil Leon Post. Kleene (1943) introduced the concepts of relative computability, foreshadowed by Turing (1939), and the arithmetical hierarchy. Kleene later generalized recursion theory to higher-order functionals. Kleene and Kreisel studied formal versions of intuitionistic mathematics, particularly in the context of proof theory.

## Subfields and scope

The *Handbook of Mathematical Logic* makes a rough division of contemporary mathematical logic into four areas:

1. set theory
2. model theory
3. recursion theory, and
4. proof theory and constructive mathematics (considered as parts of a single area).

Each area has a distinct focus, although many techniques and results are shared between multiple areas. The border lines between these fields, and the lines between mathematical logic and other fields of mathematics, are not always sharp. Gödel's incompleteness theorem marks not only a milestone in recursion theory and proof theory, but has also led to Loeb's theorem in modal logic. The method of forcing is employed in set theory, model theory, and recursion theory, as well as in the study of intuitionistic mathematics.

The mathematical field of category theory uses many formal axiomatic methods, and includes the study of categorical logic, but category theory is not ordinarily considered a subfield of mathematical logic. Because of its applicability in diverse fields of mathematics, mathematicians including Saunders Mac Lane have proposed category theory as a foundational system for mathematics, independent of set theory. These foundations use toposes, which resemble generalized models of set theory that may employ classical or nonclassical logic.

## Formal logical systems

At its core, mathematical logic deals with mathematical concepts expressed using formal logical systems. These systems, though they differ in many details, share the common property of considering only expressions in a fixed formal language, or signature. The system of first-order logic is the most widely studied today, because of its applicability to foundations of mathematics and because of its desirable proof-theoretic properties.<sup>[3]</sup> Stronger classical logics such as second-order logic or infinitary logic are also studied, along with nonclassical logics such as intuitionistic logic.

### First-order logic

**First-order logic** is a particular formal system of logic. Its syntax involves only finite expressions as well-formed formulas, while its semantics are characterized by the limitation of all quantifiers to a fixed domain of discourse.

Early results about formal logic established limitations of first-order logic. The Löwenheim–Skolem theorem (1919) showed that if a set of sentences in a countable first-order language has an infinite model then it has at least one model of each infinite cardinality. This shows that it is impossible for a set of first-order axioms to characterize the natural numbers, the real numbers, or any other infinite structure up to isomorphism. As the goal of early foundational studies was to produce axiomatic theories for all parts of mathematics, this limitation was particularly stark.

Gödel's completeness theorem (Gödel 1929) established the equivalence between semantic and syntactic definitions of logical consequence in first-order logic. It shows that if a particular sentence is true in every model that satisfies a particular set of axioms, then there must be a finite deduction of the sentence from the axioms. The compactness theorem first appeared as a lemma in Gödel's proof of the completeness theorem, and it took many years before logicians grasped its significance and began to apply it routinely. It says that a set of sentences has a model if and only if every finite subset has a model, or in other words that an inconsistent set of formulas must have a finite inconsistent subset. The completeness and compactness theorems allow for sophisticated analysis of logical consequence in first-order logic and the development of model theory, and they are a key reason for the prominence of first-order logic in mathematics.

Gödel's incompleteness theorems (Gödel 1931) establish additional limits on first-order axiomatizations. The **first incompleteness theorem** states that for any sufficiently strong, effectively given logical system there exists a

statement which is true but not provable within that system. Here a logical system is effectively given if it is possible to decide, given any formula in the language of the system, whether the formula is an axiom. A logical system is sufficiently strong if it can express the Peano axioms. When applied to first-order logic, the first incompleteness theorem implies that any sufficiently strong, consistent, effective first-order theory has models that are not elementarily equivalent, a stronger limitation than the one established by the Löwenheim–Skolem theorem. The **second incompleteness theorem** states that no sufficiently strong, consistent, effective axiom system for arithmetic can prove its own consistency, which has been interpreted to show that Hilbert's program cannot be completed.

## Other classical logics

Many logics besides first-order logic are studied. These include infinitary logics, which allow for formulas to provide an infinite amount of information, and higher-order logics, which include a portion of set theory directly in their semantics.

The most well studied infinitary logic is  $L_{\omega_1, \omega}$ . In this logic, quantifiers may only be nested to finite depths, as in first order logic, but formulas may have finite or countably infinite conjunctions and disjunctions within them. Thus, for example, it is possible to say that an object is a whole number using a formula of  $L_{\omega_1, \omega}$  such as

$$(x = 0) \vee (x = 1) \vee (x = 2) \vee \dots$$

Higher-order logics allow for quantification not only of elements of the domain of discourse, but subsets of the domain of discourse, sets of such subsets, and other objects of higher type. The semantics are defined so that, rather than having a separate domain for each higher-type quantifier to range over, the quantifiers instead range over all objects of the appropriate type. The logics studied before the development of first-order logic, for example Frege's logic, had similar set-theoretic aspects. Although higher-order logics are more expressive, allowing complete axiomatizations of structures such as the natural numbers, they do not satisfy analogues of the completeness and compactness theorems from first-order logic, and are thus less amenable to proof-theoretic analysis.

Another type of logics are fixed-point logics that allow inductive definitions, like one writes for primitive recursive functions.

One can formally define an extension of first-order logic — a notion which encompasses all logics in this section because they behave like first-order logic in certain fundamental ways, but does not encompass all logics in general, e.g. it does not encompass intuitionistic, modal or fuzzy logic. Lindström's theorem implies that the only extension of first-order logic satisfying both the Compactness theorem and the Downward Löwenheim–Skolem theorem is first-order logic.

## Nonclassical and modal logic

Modal logics include additional modal operators, such as an operator which states that a particular formula is not only true, but necessarily true. Although modal logic is not often used to axiomatize mathematics, it has been used to study the properties of first-order provability (Solovay 1976) and set-theoretic forcing (Hamkins and Löwe 2007).

Intuitionistic logic was developed by Heyting to study Brouwer's program of intuitionism, in which Brouwer himself avoided formalization. Intuitionistic logic specifically does not include the law of the excluded middle, which states that each sentence is either true or its negation is true. Kleene's work with the proof theory of intuitionistic logic showed that constructive information can be recovered from intuitionistic proofs. For example, any provably total function in intuitionistic arithmetic is computable; this is not true in classical theories of arithmetic such as Peano arithmetic.



## Algebraic logic

Algebraic logic uses the methods of abstract algebra to study the semantics of formal logics. A fundamental example is the use of Boolean algebras to represent truth values in classical propositional logic, and the use of Heyting algebras to represent truth values in intuitionistic propositional logic. Stronger logics, such as first-order logic and higher-order logic, are studied using more complicated algebraic structures such as cylindric algebras.

## Set theory

**Set theory** is the study of sets, which are abstract collections of objects. Many of the basic notions, such as ordinal and cardinal numbers, were developed informally by Cantor before formal axiomatizations of set theory were developed. The first such axiomatization, due to Zermelo (1908), was extended slightly to become Zermelo–Fraenkel set theory (ZF), which is now the most widely-used foundational theory for mathematics.

Other formalizations of set theory have been proposed, including von Neumann–Bernays–Gödel set theory (NBG), Morse–Kelley set theory (MK), and New Foundations (NF). Of these, ZF, NBG, and MK are similar in describing a cumulative hierarchy of sets. New Foundations takes a different approach; it allows objects such as the set of all sets at the cost of restrictions on its set-existence axioms. The system of Kripke–Platek set theory is closely related to generalized recursion theory.

Two famous statements in set theory are the axiom of choice and the continuum hypothesis. The axiom of choice, first stated by Zermelo (1904), was proved independent of ZF by Fraenkel (1922), but has come to be widely accepted by mathematicians. It states that given a collection of nonempty sets there is a single set  $C$  that contains exactly one element from each set in the collection. The set  $C$  is said to "choose" one element from each set in the collection. While the ability to make such a choice is considered obvious by some, since each set in the collection is nonempty, the lack of a general, concrete rule by which the choice can be made renders the axiom nonconstructive. Stefan Banach and Alfred Tarski (1924) showed that the axiom of choice can be used to decompose a solid ball into a finite number of pieces which can then be rearranged, with no scaling, to make two solid balls of the original size. This theorem, known as the Banach–Tarski paradox, is one of many counterintuitive results of the axiom of choice.

The continuum hypothesis, first proposed as a conjecture by Cantor, was listed by David Hilbert as one of his 23 problems in 1900. Gödel showed that the continuum hypothesis cannot be disproven from the axioms of Zermelo–Frankel set theory (with or without the axiom of choice), by developing the constructible universe of set theory in which the continuum hypothesis must hold. In 1963, Paul Cohen showed that the continuum hypothesis cannot be proven from the axioms of Zermelo–Frankel set theory (Cohen 1966). This independence result did not completely settle Hilbert's question, however, as it is possible that new axioms for set theory could resolve the hypothesis. Recent work along these lines has been conducted by W. Hugh Woodin, although its importance is not yet clear (Woodin 2001).

Contemporary research in set theory includes the study of large cardinals and determinacy. Large cardinals are cardinal numbers with particular properties so strong that the existence of such cardinals cannot be proved in ZFC. The existence of the smallest large cardinal typically studied, an inaccessible cardinal, already implies the consistency of ZFC. Despite the fact that large cardinals have extremely high cardinality, their existence has many ramifications for the structure of the real line. *Determinacy* refers to the possible existence of winning strategies for certain two-player games (the games are said to be *determined*). The existence of these strategies implies structural properties of the real line and other Polish spaces.

## Model theory

**Model theory** studies the models of various formal theories. Here a theory is a set of formulas in a particular formal logic and signature, while a model is a structure that gives a concrete interpretation of the theory. Model theory is closely related to universal algebra and algebraic geometry, although the methods of model theory focus more on logical considerations than those fields.

The set of all models of a particular theory is called an elementary class; classical model theory seeks to determine the properties of models in a particular elementary class, or determine whether certain classes of structures form elementary classes.

The method of quantifier elimination can be used to show that definable sets in particular theories cannot be too complicated. Tarski (1948) established quantifier elimination for real-closed fields, a result which also shows the theory of the field of real numbers is decidable. (He also noted that his methods were equally applicable to algebraically closed fields of arbitrary characteristic.) A modern subfield developing from this is concerned with o-minimal structures.

Morley's categoricity theorem, proved by Michael D. Morley (1965), states that if a first-order theory in a countable language is categorical in some uncountable cardinality, i.e. all models of this cardinality are isomorphic, then it is categorical in all uncountable cardinalities.

A trivial consequence of the continuum hypothesis is that a complete theory with less than continuum many nonisomorphic countable models can have only countably many. Vaught's conjecture, named after Robert Lawson Vaught, says that this is true even independently of the continuum hypothesis. Many special cases of this conjecture have been established.

## Recursion theory

**Recursion theory**, also called **computability theory**, studies the properties of computable functions and the Turing degrees, which divide the uncomputable functions into sets which have the same level of uncomputability. Recursion theory also includes the study of generalized computability and definability. Recursion theory grew from the work of Alonzo Church and Alan Turing in the 1930s, which was greatly extended by Kleene and Post in the 1940s.

Classical recursion theory focuses on the computability of functions from the natural numbers to the natural numbers. The fundamental results establish a robust, canonical class of computable functions with numerous independent, equivalent characterizations using Turing machines,  $\lambda$  calculus, and other systems. More advanced results concern the structure of the Turing degrees and the lattice of recursively enumerable sets.

Generalized recursion theory extends the ideas of recursion theory to computations that are no longer necessarily finite. It includes the study of computability in higher types as well as areas such as hyperarithmetical theory and  $\alpha$ -recursion theory.

Contemporary research in recursion theory includes the study of applications such as algorithmic randomness and computable model theory as well as new results in pure recursion theory.

## Algorithmically unsolvable problems

An important subfield of recursion theory studies algorithmic unsolvability; a problem is **algorithmically unsolvable** if there is no computable function which, given any [code for an] instance of the problem, returns the correct answer. The first results about unsolvability, obtained independently by Church and Turing in 1936, showed that the Entscheidungsproblem is algorithmically unsolvable. Turing proved this by establishing the unsolvability of the halting problem, a result with far-ranging implications in both recursion theory and computer science.

There are many known examples of undecidable problems from ordinary mathematics. The word problem for groups was proved algorithmically unsolvable by Pyotr Novikov in 1955 and independently by W. Boone in 1959. The busy

beaver problem, developed by Tibor Radó in 1962, is another well-known example.

Hilbert's tenth problem asked for an algorithm to determine whether a multivariate polynomial equation with integer coefficients has a solution in the integers. Partial progress was made by Julia Robinson, Martin Davis and Hilary Putnam. The algorithmic unsolvability of the problem was proved by Yuri Matiyasevich in 1970 (Davis 1973).

## Proof theory and constructive mathematics

**Proof theory** is the study of formal proofs in various logical deduction systems. These proofs are represented as formal mathematical objects, facilitating their analysis by mathematical techniques. Several deduction systems are commonly considered, including Hilbert-style deduction systems, systems of natural deduction, and the sequent calculus developed by Gentzen.

The study of **constructive mathematics**, in the context of mathematical logic, includes the study of systems in non-classical logic such as intuitionistic logic, as well as the study of predicative systems. An early proponent of predicativism was Hermann Weyl, who showed it is possible to develop a large part of real analysis using only predicative methods (Weyl 1918).

Because proofs are entirely finitary, whereas truth in a structure is not, it is common for work in constructive mathematics to emphasize provability. The relationship between provability in classical (or nonconstructive) systems and provability in intuitionistic (or constructive, respectively) systems is of particular interest. Results such as the Gödel–Gentzen negative translation show that it is possible to embed (or *translate*) classical logic into intuitionistic logic, allowing some properties about intuitionistic proofs to be transferred back to classical proofs.

Recent developments in proof theory include the study of proof mining by Ulrich Kohlenbach and the study of proof-theoretic ordinals by Michael Rathjen.

## Connections with computer science

The study of computability theory in computer science is closely related to the study of computability in mathematical logic. There is a difference of emphasis, however. Computer scientists often focus on concrete programming languages and feasible computability, while researchers in mathematical logic often focus on computability as a theoretical concept and on noncomputability.

The theory of semantics of programming languages is related to model theory, as is program verification (in particular, model checking). The Curry–Howard isomorphism between proofs and programs relates to proof theory, especially intuitionistic logic. Formal calculi such as the lambda calculus and combinatory logic are now studied as idealized programming languages.

Computer science also contributes to mathematics by developing techniques for the automatic checking or even finding of proofs, such as automated theorem proving and logic programming.

Descriptive complexity theory relates logics to computational complexity. The first significant result in this area, Fagin's theorem (1974) established that NP is precisely the set of languages expressible by sentences of existential second-order logic.

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## Foundations of mathematics

In the 19th century, mathematicians became aware of logical gaps and inconsistencies in their field. It was shown that Euclid's axioms for geometry, which had been taught for centuries as an example of the axiomatic method, were incomplete. The use of infinitesimals, and the very definition of function, came into question in analysis, as pathological examples such as Weierstrass' nowhere-differentiable continuous function were discovered.

Cantor's study of arbitrary infinite sets also drew criticism. Leopold Kronecker famously stated "God made the integers; all else is the work of man," endorsing a return to the study of finite, concrete objects in mathematics. Although Kronecker's argument was carried forward by constructivists in the 20th century, the mathematical community as a whole rejected them. David Hilbert argued in favor of the study of the infinite, saying "No one shall expel us from the Paradise that Cantor has created."

Mathematicians began to search for axiom systems that could be used to formalize large parts of mathematics. In addition to removing ambiguity from previously-naïve terms such as function, it was hoped that this axiomatization would allow for consistency proofs. In the 19th century, the main method of proving the consistency of a set of axioms was to provide a model for it. Thus, for example, non-Euclidean geometry can be proved consistent by defining *point* to mean a point on a fixed sphere and *line* to mean a great circle on the sphere. The resulting structure, a model of elliptic geometry, satisfies the axioms of plane geometry except the parallel postulate.

With the development of formal logic, Hilbert asked whether it would be possible to prove that an axiom system is consistent by analyzing the structure of possible proofs in the system, and showing through this analysis that it is impossible to prove a contradiction. This idea led to the study of proof theory. Moreover, Hilbert proposed that the analysis should be entirely concrete, using the term *finitary* to refer to the methods he would allow but not precisely defining them. This project, known as Hilbert's program, was seriously affected by Gödel's incompleteness theorems, which show that the consistency of formal theories of arithmetic cannot be established using methods formalizable in those theories. Gentzen showed that it is possible to produce a proof of the consistency of arithmetic in a finitary system augmented with axioms of transfinite induction, and the techniques he developed to so do were seminal in proof theory.

A second thread in the history of foundations of mathematics involves nonclassical logics and constructive mathematics. The study of constructive mathematics includes many different programs with various definitions of *constructive*. At the most accommodating end, proofs in ZF set theory that do not use the axiom of choice are called constructive by many mathematicians. More limited versions of constructivism limit themselves to natural numbers, number-theoretic functions, and sets of natural numbers (which can be used to represent real numbers, facilitating the study of mathematical analysis). A common idea is that a concrete means of computing the values of the function must be known before the function itself can be said to exist.

In the early 20th century, Luitzen Egbertus Jan Brouwer founded intuitionism as a philosophy of mathematics. This philosophy, poorly understood at first, stated that in order for a mathematical statement to be true to a mathematician, that person must be able to *intuit* the statement, to not only believe its truth but understand the reason for its truth. A consequence of this definition of truth was the rejection of the law of the excluded middle, for there are statements that, according to Brouwer, could not be claimed to be true while their negations also could not be claimed true. Brouwer's philosophy was influential, and the cause of bitter disputes among prominent mathematicians. Later, Kleene and Kreisel would study formalized versions of intuitionistic logic (Brouwer rejected formalization, and presented his work in unformalized natural language). With the advent of the BHK interpretation and Kripke models, intuitionism became easier to reconcile with classical mathematics.

## See also

- List of mathematical logic topics
- List of computability and complexity topics
- List of set theory topics
- List of first-order theories
- Knowledge representation
- Metalogic

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## External links

- Mathematical Logic around the world <sup>[25]</sup>
- Polyvalued logic <sup>[26]</sup>
- *forall x: an introduction to formal logic* <sup>[27]</sup>, by P.D. Magnus, is a free textbook.
- *A Problem Course in Mathematical Logic* <sup>[28]</sup>, by Stefan Bilaniuk, is another free textbook.
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- Stanford Encyclopedia of Philosophy: Classical Logic <sup>[30]</sup> – by Stewart Shapiro.
- Stanford Encyclopedia of Philosophy: First-order Model Theory <sup>[31]</sup> – by Wilfrid Hodges.
- The London Philosophy Study Guide <sup>[32]</sup> offers many suggestions on what to read, depending on the student's familiarity with the subject:
  - Mathematical Logic <sup>[33]</sup>

- Set Theory & Further Logic <sup>[34]</sup>
- Philosophy of Mathematics <sup>[35]</sup>

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# Topology

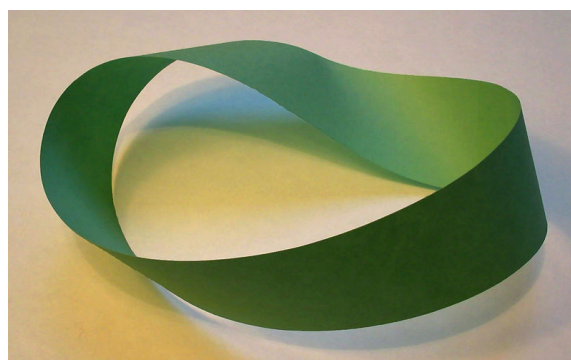
**Topology** (from the Greek τόπος, “place”, and λόγος, “study”) is a major area of mathematics concerned with spatial properties that are preserved under continuous deformations of objects, for example, deformations that involve stretching, but no tearing or gluing. It emerged through the development of concepts from geometry and set theory, such as space, dimension, and transformation.

Ideas that are now classified as topological were expressed as early as 1736, and toward the end of the 19th century, a distinct discipline developed, which was referred to in Latin as the *geometria situs* (“geometry of place”) or *analysis situs* (Greek-Latin for “picking apart of place”), and which later acquired the modern name of topology. By the middle of the 20<sup>th</sup> century, topology had become an important area of study within mathematics.

The word *topology* is used both for the mathematical discipline and for a family of sets with certain properties that are used to define a topological space, a basic object of topology. Of particular importance are *homeomorphisms*, which can be defined as continuous functions with a continuous inverse. For instance, the function  $y = x^3$  is a homeomorphism of the real line.

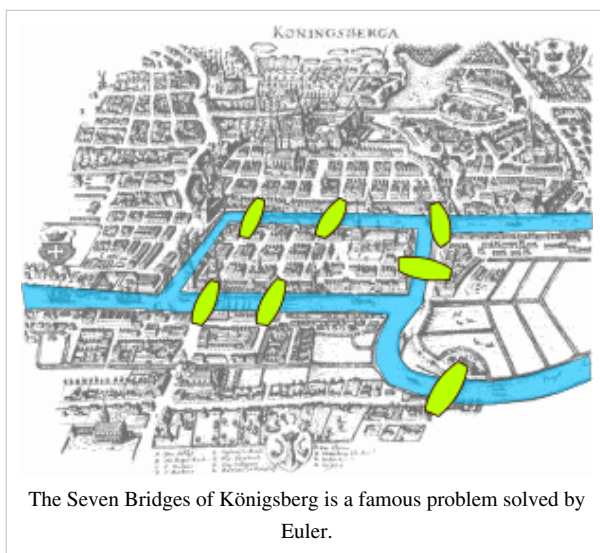
Topology includes many subfields. The most basic and traditional division within topology is **point-set topology**, which establishes the foundational aspects of topology and investigates concepts inherent to topological spaces (basic examples include compactness and connectedness); **algebraic topology**, which generally tries to measure degrees of connectivity using algebraic constructs such as homotopy groups and homology; and **geometric topology**, which primarily studies manifolds and their embeddings (placements) in other manifolds. Some of the most active areas, such as low dimensional topology and graph theory, do not fit neatly in this division.

See also: topology glossary for definitions of some of the terms used in topology and topological space for a more technical treatment of the subject.



A Möbius strip, an object with only one surface and one edge.  
Such shapes are an object of study in topology.

## History



Topology began with the investigation of certain questions in geometry. Euler's 1736 paper on *Seven Bridges of Königsberg* is regarded as one of the first academic treatises in modern topology.

The term "Topologie" was introduced in German in 1847 by Johann Benedict Listing in *Vorstudien zur Topologie*, Vandenhoeck und Ruprecht, Göttingen, pp. 67, 1848, who had used the word for ten years in correspondence before its first appearance in print. "Topology," its English form, was introduced in 1883 in the journal *Nature* to distinguish "qualitative geometry from the ordinary geometry in which quantitative relations chiefly are treated". The term **topologist** in the sense of a specialist in topology was used in 1905 in the magazine *Spectator*. However, none of these uses corresponds

exactly to the modern definition of topology.

Modern topology depends strongly on the ideas of set theory, developed by Georg Cantor in the later part of the 19th century. Cantor, in addition to setting down the basic ideas of set theory, considered point sets in Euclidean space, as part of his study of Fourier series.

Henri Poincaré published *Analysis Situs* in 1895, introducing the concepts of homotopy and homology, which are now considered part of algebraic topology.

Maurice Fréchet, unifying the work on function spaces of Cantor, Volterra, Arzelà, Hadamard, Ascoli, and others, introduced the metric space in 1906. A metric space is now considered a special case of a general topological space. In 1914, Felix Hausdorff coined the term "topological space" and gave the definition for what is now called a Hausdorff space. In current usage, a topological space is a slight generalization of Hausdorff spaces, given in 1922 by Kazimierz Kuratowski.

For further developments, see point-set topology and algebraic topology.

## Elementary introduction

Topology, as a branch of mathematics, can be formally defined as "the study of qualitative properties of certain objects (called topological spaces) that are invariant under certain kind of transformations (called continuous maps), especially those properties that are invariant under a certain kind of equivalence (called homeomorphism)."

The term *topology* is also used to refer to a structure imposed upon a set  $X$ , a structure which essentially 'characterizes' the set  $X$  as a topological space by taking proper care of properties such as convergence, connectedness and continuity, upon transformation.

Topological spaces show up naturally in almost every branch of mathematics. This has made topology one of the great unifying ideas of mathematics.

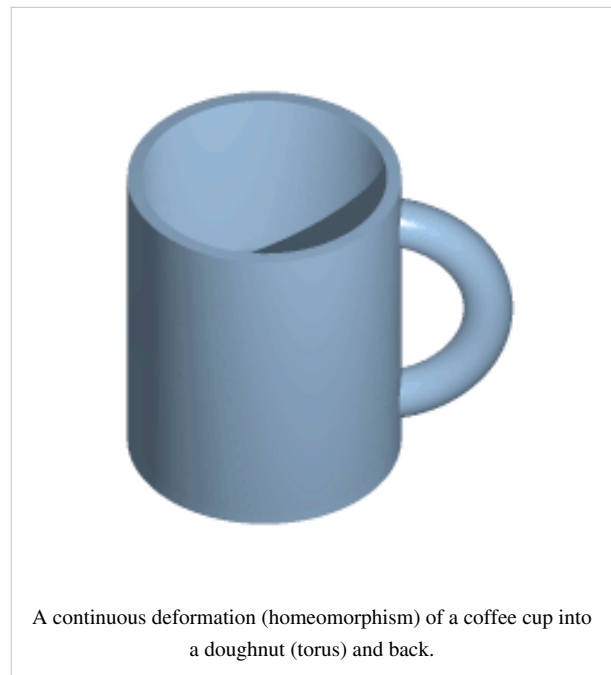
The motivating insight behind topology is that some geometric problems depend not on the exact shape of the objects involved, but rather on the way they are put together. For example, the square and the circle have many properties in common: they are both one dimensional objects (from a topological point of view) and both separate the plane into two parts, the part inside and the part outside.

One of the first papers in topology was the demonstration, by Leonhard Euler, that it was impossible to find a route through the town of Königsberg (now Kaliningrad) that would cross each of its seven bridges exactly once. This result did not depend on the lengths of the bridges, nor on their distance from one another, but only on connectivity

properties: which bridges are connected to which islands or riverbanks. This problem, the *Seven Bridges of Königsberg*, is now a famous problem in introductory mathematics, and led to the branch of mathematics known as graph theory.

Similarly, the hairy ball theorem of algebraic topology says that "one cannot comb the hair flat on a hairy ball without creating a cowlick." This fact is immediately convincing to most people, even though they might not recognize the more formal statement of the theorem, that there is no nonvanishing continuous tangent vector field on the sphere. As with the *Bridges of Königsberg*, the result does not depend on the exact shape of the sphere; it applies to pear shapes and in fact any kind of smooth blob, as long as it has no holes.

In order to deal with these problems that do not rely on the exact shape of the objects, one must be clear about just what properties these problems *do* rely on. From this need arises the notion of homeomorphism. The impossibility of crossing each bridge just once applies to any arrangement of bridges homeomorphic to those in Königsberg, and the hairy ball theorem applies to any space homeomorphic to a sphere.



Intuitively two spaces are homeomorphic if one can be deformed into the other without cutting or gluing. A traditional joke is that a topologist can't distinguish a coffee mug from a doughnut, since a sufficiently pliable doughnut could be reshaped to the form of a coffee cup by creating a dimple and progressively enlarging it, while shrinking the hole into a handle. A precise definition of homeomorphic, involving a continuous function with a continuous inverse, is necessarily more technical.

Homeomorphism can be considered the most basic *topological equivalence*. Another is homotopy equivalence. This is harder to describe without getting technical, but the essential notion is that two objects are homotopy equivalent if they both result from "squishing" some larger object.

Equivalence classes of the English alphabet in uppercase sans-serif font (Myriad); left - homeomorphism, right - homotopy equivalence

{A, R} {B} {C, G, I, J, L, M, N, S, U, V, W, Z}  
{D, O} {E, F, T, Y} {H, K} {P, Q} {X}

{A, R, D, O, P, Q} {B}  
{C, E, F, G, H, I, J, K, L, M, N, S, T, U, V, W, X, Y, Z}

An introductory exercise is to classify the uppercase letters of the English alphabet according to homeomorphism and homotopy equivalence. The result depends partially on the font used. The figures use a sans-serif font named Myriad. Notice that homotopy equivalence is a rougher relationship than homeomorphism; a homotopy equivalence class can contain several of the homeomorphism classes. The simple case of homotopy equivalence described above can be used here to show two letters are homotopy equivalent, e.g. O fits inside P and the tail of the P can be squished to the "hole" part.

Thus, the homeomorphism classes are: one hole two tails, two holes no tail, no holes, one hole no tail, no holes three tails, a bar with four tails (the "bar" on the K is almost too short to see), one hole one tail, and no holes four tails.

The homotopy classes are larger, because the tails can be squished down to a point. The homotopy classes are: one hole, two holes, and no holes.

To be sure we have classified the letters correctly, we not only need to show that two letters in the same class are equivalent, but that two letters in different classes are not equivalent. In the case of homeomorphism, this can be done by suitably selecting points and showing their removal disconnects the letters differently. For example, X and Y are not homeomorphic because removing the center point of the X leaves four pieces; whatever point in Y corresponds to this point, its removal can leave at most three pieces. The case of homotopy equivalence is harder and requires a more elaborate argument showing an algebraic invariant, such as the fundamental group, is different on the supposedly differing classes.

Letter topology has some practical relevance in stencil typography. The font Braggadocio, for instance, has stencils that are made of one connected piece of material.

## Mathematical definition

Let  $X$  be any set and let  $T$  be a family of subsets of  $X$ . Then  $T$  is a **topology** on  $X$  iff

1. Both the empty set and  $X$  are elements of  $T$ .
2. Any union of arbitrarily many elements of  $T$  is an element of  $T$ .
3. Any intersection of finitely many elements of  $T$  is an element of  $T$ .

If  $T$  is a topology on  $X$ , then the pair  $(X, T)$  is called a **topological space**, and the notation  $X_T$  is used to denote a set  $X$  endowed with the particular topology  $T$ .

The **open** sets in  $X$  are defined to be the members of  $T$ ; note that in general not all subsets of  $X$  need be in  $T$ . A subset of  $X$  is said to be closed if its complement is in  $T$  (i.e., its complement is open). A subset of  $X$  may be open, closed, both, or neither.

A function or map from one topological space to another is called **continuous** if the inverse image of any open set is open. If the function maps the real numbers to the real numbers (both spaces with the Standard Topology), then this definition of continuous is equivalent to the definition of continuous in calculus. If a continuous function is one-to-one and onto and if the inverse of the function is also continuous, then the function is called a homeomorphism and the domain of the function is said to be homeomorphic to the range. Another way of saying this is that the function has a natural extension to the topology. If two spaces are homeomorphic, they have identical topological properties, and are considered to be topologically the same. The cube and the sphere are homeomorphic, as are the coffee cup and the doughnut. But the circle is not homeomorphic to the doughnut.

## Topology topics

### Some theorems in general topology

- Every closed interval in  $\mathbf{R}$  of finite length is compact. More is true: In  $\mathbf{R}^n$ , a set is compact if and only if it is closed and bounded. (See Heine-Borel theorem).
- Every continuous image of a compact space is compact.
- Tychonoff's theorem: The (arbitrary) product of compact spaces is compact.
- A compact subspace of a Hausdorff space is closed.
- Every continuous bijection from a compact space to a Hausdorff space is necessarily a homeomorphism.
- Every sequence of points in a compact metric space has a convergent subsequence.
- Every interval in  $\mathbf{R}$  is connected.
- Every compact  $m$ -manifold can be embedded in some Euclidean space  $\mathbf{R}^n$ .
- The continuous image of a connected space is connected.
- A metric space is Hausdorff, also normal and paracompact.

- The metrization theorems provide necessary and sufficient conditions for a topology to come from a metric.
- The Tietze extension theorem: In a normal space, every continuous real-valued function defined on a closed subspace can be extended to a continuous map defined on the whole space.
- Any open subspace of a Baire space is itself a Baire space.
- The Baire category theorem: If  $X$  is a complete metric space or a locally compact Hausdorff space, then the interior of every union of countably many nowhere dense sets is empty.
- On a paracompact Hausdorff space every open cover admits a partition of unity subordinate to the cover.
- Every path-connected, locally path-connected and semi-locally simply connected space has a universal cover.

General topology also has some surprising connections to other areas of mathematics. For example:

- In number theory, Furstenberg's proof of the infinitude of primes.

See also some counter-intuitive theorems, e.g. the Banach-Tarski one.

### Some useful notions from algebraic topology

See also list of algebraic topology topics.

- Homology and cohomology: Betti numbers, Euler characteristic, degree of a continuous mapping.
- Operations: cup product, Massey product
- Intuitively-attractive applications: Brouwer fixed-point theorem, Hairy ball theorem, Borsuk-Ulam theorem, Ham sandwich theorem.
- Homotopy groups (including the fundamental group).
- Chern classes, Stiefel-Whitney classes, Pontryagin classes.

### Generalizations

Occasionally, one needs to use the tools of topology but a "set of points" is not available. In pointless topology one considers instead the lattice of open sets as the basic notion of the theory, while Grothendieck topologies are certain structures defined on arbitrary categories which allow the definition of sheaves on those categories, and with that the definition of quite general cohomology theories.

### Topology in art and literature

- Some M. C. Escher works illustrate topological concepts, such as Möbius strips and non-orientable spaces.

### See also

- List of algebraic topology topics
- List of general topology topics
- List of geometric topology topics
- Publications in topology
- List of topology topics
- Topology glossary

## References

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- Richeson, David S. (2008) *Euler's Gem: The Polyhedron Formula and the Birth of Topology*. Princeton University Press.
- Willard, Stephen (2004). *General Topology*. Dover Publications. ISBN 0-486-43479-6.

## External links

- Elementary Topology: A First Course <sup>[1]</sup> Viro, Ivanov, Netsvetaev, Kharlamov
- Topology <sup>[2]</sup> at the Open Directory Project
- The Topological Zoo <sup>[3]</sup> at The Geometry Center
- Topology Atlas <sup>[4]</sup>
- Topology Course Lecture Notes <sup>[5]</sup> Aisling McCluskey and Brian McMaster, Topology Atlas
- Topology Glossary <sup>[6]</sup>
- Moscow 1935: Topology moving towards America <sup>[7]</sup>, a historical essay by Hassler Whitney.

## References

- [1] <http://www.pdmi.ras.ru/~olegviro/topoman/index.html>
- [2] <http://www.dmoz.org/Science/Math/Topology/>
- [3] <http://www.geom.uiuc.edu/zoo/>
- [4] <http://at.yorku.ca/topology/>
- [5] <http://at.yorku.ca/i/a/a/b/23.htm>
- [6] <http://www.ornl.gov/sci/ortep/topology/defs.txt>
- [7] [http://www.ams.org/online\\_bks/hmath1/hmath1-whitney10.pdf](http://www.ams.org/online_bks/hmath1/hmath1-whitney10.pdf)

# Epigenetic landscape

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**Epigenetic landscape** is a metaphor for biological development. Its originator, Conrad Hal Waddington, said that cell fates were established in development much like a marble rolls down to the point of lowest local elevation. Waddington suggested visualising increasing irreversibility of cell type differentiation as ridges rising between the valleys where the marbles (cells) are travelling.

Today, the term refers to the combined epigenetic modifications of a given domain of DNA sequence. Epigenetic modifications include methylation of cytosine residues of DNA and post-translational modifications of the histone proteins associated with the DNA strand. The specific combination of epigenetic modifications determines the conformation of the chromatin fibre into which the DNA and histones are packaged, and can thereby regulate the transcriptional potential of the underlying genes.

## See also

- Epigenetics

# Network theory

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**Network theory** is an area of computer science and network science and part of graph theory. It has application in many disciplines including particle physics, computer science, biology, economics, operations research, and sociology. Network theory concerns itself with the study of graphs as a representation of either symmetric relations or, more generally, of asymmetric relations between discrete objects. Applications of network theory include logistical networks, the World Wide Web, gene regulatory networks, metabolic networks, social networks, epistemological networks, etc. See list of network theory topics for more examples.

## Network optimization

Network problems that involve finding an optimal way of doing something are studied under the name of combinatorial optimization. Examples include network flow, shortest path problem, transport problem, transshipment problem, location problem, matching problem, assignment problem, packing problem, routing problem, Critical Path Analysis and PERT (Program Evaluation & Review Technique).

## Network analysis

### Social network analysis

**Social network analysis** maps relationships between individuals in social networks.<sup>[1]</sup> Such individuals are often persons, but may be groups (including cliques and cohesive blocks <sup>[2]</sup>), organizations, nation states, web sites, or citations between scholarly publications (scientometrics).

Network analysis, and its close cousin traffic analysis, has significant use in intelligence. By monitoring the communication patterns between the network nodes, its structure can be established. This can be used for uncovering insurgent networks of both hierarchical and leaderless nature.

## Biological network analysis

With the recent explosion of publicly available high throughput biological data, the analysis of molecular networks has gained significant interest. The type of analysis in this content are closely related to social network analysis, but often focusing on local patterns in the network. For example network motifs are small subgraphs that are over-represented in the network. Activity motifs are similar over-represented patterns in the attributes of nodes and edges in the network that are over represented given the network structure.

## Link analysis

Link analysis is a subset of network analysis, exploring associations between objects. An example may be examining the addresses of suspects and victims, the telephone numbers they have dialed and financial transactions that they have partaken in during a given timeframe, and the familial relationships between these subjects as a part of police investigation. Link analysis here provides the crucial relationships and associations between very many objects of different types that are not apparent from isolated pieces of information. Computer-assisted or fully automatic computer-based link analysis is increasingly employed by banks and insurance agencies in fraud detection, by telecommunication operators in telecommunication network analysis, by medical sector in epidemiology and pharmacology, in law enforcement investigations, by search engines for relevance rating (and conversely by the spammers for spamdexing and by business owners for search engine optimization), and everywhere else where relationships between many objects have to be analyzed.

## Web link analysis

Several Web search ranking algorithms use link-based centrality metrics, including (in order of appearance) Marchiori's Hyper Search, Google's PageRank, Kleinberg's HITS algorithm, and the TrustRank algorithm. Link analysis is also conducted in information science and communication science in order to understand and extract information from the structure of collections of web pages. For example the analysis might be of the interlinking between politicians' web sites or blogs.

## Centrality measures

Information about the relative importance of nodes and edges in a graph can be obtained through centrality measures, widely used in disciplines like sociology. For example, eigenvector centrality uses the eigenvectors of the adjacency matrix to determine nodes that tend to be frequently visited.

## Spread of content in networks

Content in a complex network can spread via two major methods: conserved spread and non-conserved spread.<sup>[3]</sup> In conserved spread, the total amount of content that enters a complex network remains constant as it passes through. The model of conserved spread can best be represented by a pitcher containing a fixed amount of water being poured into a series of funnels connected by tubes . Here, the pitcher represents the original source and the water is the content being spread. The funnels and connecting tubing represent the nodes and the connections between nodes, respectively. As the water passes from one funnel into another, the water disappears instantly from the funnel that was previously exposed to the water. In non-conserved spread, the amount of content changes as it enters and passes through a complex network. The model of non-conserved spread can best be represented by a continuously running faucet running through a series of funnels connected by tubes . Here, the amount of water from the original source is infinite. Also, any funnels that have been exposed to the water continue to experience the water even as it passes into successive funnels. The non-conserved model is the most suitable for explaining the transmission of most infectious diseases.



## See also

- Complex network
- Network science
- Network topology
- Small-world networks
- Social circles
- Scale-free networks
- Sequential dynamical systems

## Implementations

- Orange, a free data mining software suite, module orngNetwork<sup>[4]</sup>
- Pajek<sup>[5]</sup>, program for (large) network analysis and visualization

## External links

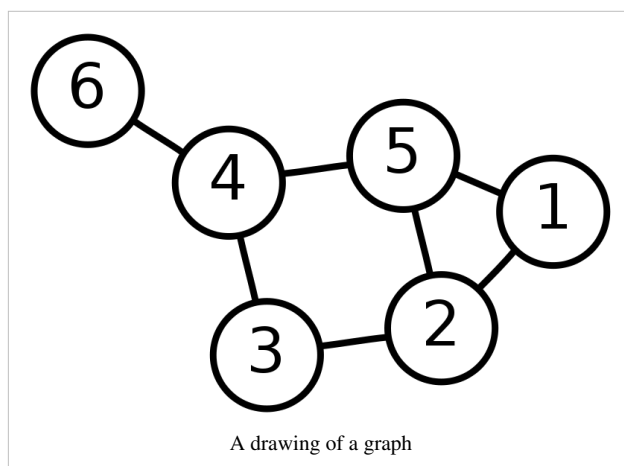
- netwiki<sup>[6]</sup> Scientific wiki dedicated to network theory
- New Network Theory<sup>[7]</sup> International Conference on 'New Network Theory'
- Network Workbench<sup>[8]</sup>: A Large-Scale Network Analysis, Modeling and Visualization Toolkit
- Network analysis of computer networks<sup>[9]</sup>
- Network analysis of organizational networks<sup>[10]</sup>
- Network analysis of terrorist networks<sup>[11]</sup>
- Network analysis of a disease outbreak<sup>[12]</sup>
- Link Analysis: An Information Science Approach<sup>[13]</sup> (book)
- Connected: The Power of Six Degrees<sup>[14]</sup> (documentary)

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- [2] [http://intersci.ss.uci.edu/wiki/index.php/Cohesive\\_blocking](http://intersci.ss.uci.edu/wiki/index.php/Cohesive_blocking)
- [3] Newman, M., Barabási, A.-L., Watts, D.J. [eds.] (2006) *The Structure and Dynamics of Networks*. Princeton, N.J.: Princeton University Press.
- [4] <http://www.ailab.si/orange/doc/modules/orngNetwork.htm>
- [5] <http://pajek.imfm.si/doku.php>
- [6] <http://netwiki.amath.unc.edu/>
- [7] <http://www.networkcultures.org/networktheory/>
- [8] <http://nwb.slis.indiana.edu/>
- [9] <http://www.orgnet.com/SocialLifeOfRouters.pdf>
- [10] <http://www.orgnet.com/orgnetmap.pdf>
- [11] <http://firstmonday.org/htbin/cgiwrap/bin/ojs/index.php/fm/article/view/941/863>
- [12] <http://www.orgnet.com/AJPH2007.pdf>
- [13] <http://linkanalysis.wlv.ac.uk/>
- [14] <http://gephi.org/2008/how-kevin-bacon-cured-cancer/>

# Graph theory

In mathematics and computer science, **graph theory** is the study of *graphs*: mathematical structures used to model pairwise relations between objects from a certain collection. A "graph" in this context refers to a collection of vertices or 'nodes' and a collection of *edges* that connect pairs of vertices. A graph may be *undirected*, meaning that there is no distinction between the two vertices associated with each edge, or its edges may be *directed* from one vertex to another; see graph (mathematics) for more detailed definitions and for other variations in the types of graphs that are commonly considered. The graphs studied in graph theory should not be confused with "graphs of functions" and other kinds of graphs.

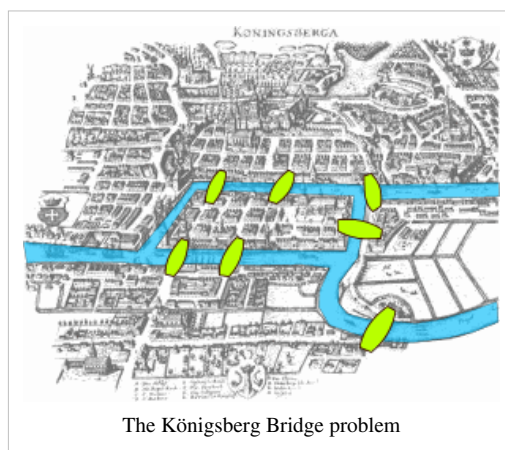


Refer to Glossary of graph theory for basic definitions in graph theory.

## History

The paper written by Leonhard Euler on the *Seven Bridges of Königsberg* and published in 1736 is regarded as the first paper in the history of graph theory.<sup>[1]</sup> This paper, as well as the one written by Vandermonde on the *knight problem*, carried on with the *analysis situs* initiated by Leibniz. Euler's formula relating the number of edges, vertices, and faces of a convex polyhedron was studied and generalized by Cauchy<sup>[2]</sup> and L'Huillier,<sup>[3]</sup> and is at the origin of topology.

More than one century after Euler's paper on the bridges of Königsberg and while Listing introduced topology, Cayley was led by the study of particular analytical forms arising from differential calculus to study a particular class of graphs, the *trees*. This study



had many implications in theoretical chemistry. The involved techniques mainly concerned the enumeration of graphs having particular properties. Enumerative graph theory then rose from the results of Cayley and the fundamental results published by Pólya between 1935 and 1937 and the generalization of these by De Bruijn in 1959. Cayley linked his results on trees with the contemporary studies of chemical composition.<sup>[4]</sup> The fusion of the ideas coming from mathematics with those coming from chemistry is at the origin of a part of the standard terminology of graph theory.

In particular, the term "graph" was introduced by Sylvester in a paper published in 1878 in *Nature*, where he draws an analogy between "quantic invariants" and "co-variants" of algebra and molecular diagrams:<sup>[5]</sup>

"[...] Every invariant and co-variant thus becomes expressible by a *graph* precisely identical with a Kekuléan diagram or chemicograph. [...] I give a rule for the geometrical multiplication of graphs, *i.e.* for constructing a *graph* to the product of in- or co-variants whose separate graphs are given. [...]" (italics as in the original).

One of the most famous and productive problems of graph theory is the four color problem: "Is it true that any map drawn in the plane may have its regions colored with four colors, in such a way that any two regions having a

common border have different colors?" This problem was first posed by Francis Guthrie in 1852 and its first written record is in a letter of De Morgan addressed to Hamilton the same year. Many incorrect proofs have been proposed, including those by Cayley, Kempe, and others. The study and the generalization of this problem by Tait, Heawood, Ramsey and Hadwiger led to the study of the colorings of the graphs embedded on surfaces with arbitrary genus. Tait's reformulation generated a new class of problems, the *factorization problems*, particularly studied by Petersen and König. The works of Ramsey on colorations and more specially the results obtained by Turán in 1941 was at the origin of another branch of graph theory, *extremal graph theory*.

The four color problem remained unsolved for more than a century. A proof produced in 1976 by Kenneth Appel and Wolfgang Haken,<sup>[6] [7]</sup> which involved checking the properties of 1,936 configurations by computer, was not fully accepted at the time due to its complexity. A simpler proof considering only 633 configurations was given twenty years later by Robertson, Seymour, Sanders and Thomas.<sup>[8]</sup>

The autonomous development of topology from 1860 and 1930 fertilized graph theory back through the works of Jordan, Kuratowski and Whitney. Another important factor of common development of graph theory and topology came from the use of the techniques of modern algebra. The first example of such a use comes from the work of the physicist Gustav Kirchhoff, who published in 1845 his Kirchhoff's circuit laws for calculating the voltage and current in electric circuits.

The introduction of probabilistic methods in graph theory, especially in the study of Erdős and Rényi of the asymptotic probability of graph connectivity, gave rise to yet another branch, known as *random graph theory*, which has been a fruitful source of graph-theoretic results.

## Drawing graphs

Graphs are represented graphically by drawing a dot for every vertex, and drawing an arc between two vertices if they are connected by an edge. If the graph is directed, the direction is indicated by drawing an arrow.

A graph drawing should not be confused with the graph itself (the abstract, non-visual structure) as there are several ways to structure the graph drawing. All that matters is which vertices are connected to which others by how many edges and not the exact layout. In practice it is often difficult to decide if two drawings represent the same graph. Depending on the problem domain some layouts may be better suited and easier to understand than others.

## Graph-theoretic data structures

There are different ways to store graphs in a computer system. The data structure used depends on both the graph structure and the algorithm used for manipulating the graph. Theoretically one can distinguish between list and matrix structures but in concrete applications the best structure is often a combination of both. List structures are often preferred for sparse graphs as they have smaller memory requirements. Matrix structures on the other hand provide faster access for some applications but can consume huge amounts of memory.

### List structures

#### Incidence list

The edges are represented by an array containing pairs (ordered if directed) of vertices (that the edge connects) and possibly weight and other data. Vertices connected by an edge are said to be *adjacent*.

#### Adjacency list

Much like the incidence list, each vertex has a list of which vertices it is adjacent to. This causes redundancy in an undirected graph: for example, if vertices A and B are adjacent, A's adjacency list contains B, while B's list contains A. Adjacency queries are faster, at the cost of extra storage space.

## Matrix structures

### Incidence matrix

The graph is represented by a matrix of size  $|V|$  (number of vertices) by  $|E|$  (number of edges) where the entry [vertex, edge] contains the edge's endpoint data (simplest case: 1 - connected, 0 - not connected).

### Adjacency matrix

This is the  $n$  by  $n$  matrix  $A$ , where  $n$  is the number of vertices in the graph. If there is an edge from some vertex  $x$  to some vertex  $y$ , then the element  $a_{x,y}$  is 1 (or in general the number of  $xy$  edges), otherwise it is 0. In computing, this matrix makes it easy to find subgraphs, and to reverse a directed graph.

### Laplacian matrix or Kirchhoff matrix or Admittance matrix

This is defined as  $D - A$ , where  $D$  is the diagonal degree matrix. It explicitly contains both adjacency information and degree information.

### Distance matrix

A symmetric  $n$  by  $n$  matrix  $D$  whose element  $d_{x,y}$  is the length of a shortest path between  $x$  and  $y$ ; if there is no such path  $d_{x,y} = \text{infinity}$ . It can be derived from powers of  $A$

$$d_{x,y} = \min \{n \mid A^n[x, y] \neq 0\}.$$

## Problems in graph theory

### Enumeration

There is a large literature on graphical enumeration: the problem of counting graphs meeting specified conditions. Some of this work is found in Harary and Palmer (1973).

### Subgraphs, induced subgraphs, and minors

A common problem, called the subgraph isomorphism problem, is finding a fixed graph as a subgraph in a given graph. One reason to be interested in such a question is that many graph properties are *hereditary* for subgraphs, which means that a graph has the property if and only if all subgraphs have it too. Unfortunately, finding maximal subgraphs of a certain kind is often an NP-complete problem.

- Finding the largest complete graph is called the clique problem (NP-complete).

A similar problem is finding induced subgraphs in a given graph. Again, some important graph properties are hereditary with respect to induced subgraphs, which means that a graph has a property if and only if all induced subgraphs also have it. Finding maximal induced subgraphs of a certain kind is also often NP-complete. For example,

- Finding the largest edgeless induced subgraph, or independent set, called the independent set problem (NP-complete).

Still another such problem, the *minor containment problem*, is to find a fixed graph as a minor of a given graph. A minor or **subcontraction** of a graph is any graph obtained by taking a subgraph and contracting some (or no) edges. Many graph properties are hereditary for minors, which means that a graph has a property if and only if all minors have it too. A famous example:

- A graph is planar if it contains as a minor neither the complete bipartite graph  $K_{3,3}$  (See the Three-cottage problem) nor the complete graph  $K_5$ .

Another class of problems has to do with the extent to which various species and generalizations of graphs are determined by their *point-deleted subgraphs*, for example:

- The reconstruction conjecture

## Graph coloring

Many problems have to do with various ways of coloring graphs, for example:

- The four-color theorem
- The strong perfect graph theorem
- The Erdős–Faber–Lovász conjecture (unsolved)
- The total coloring conjecture (unsolved)
- The list coloring conjecture (unsolved)
- The Hadwiger conjecture (graph theory) (unsolved)

## Route problems

- Hamiltonian path and cycle problems
- Minimum spanning tree
- Route inspection problem (also called the "Chinese Postman Problem")
- Seven Bridges of Königsberg
- Shortest path problem
- Steiner tree
- Three-cottage problem
- Traveling salesman problem (NP-complete)

## Network flow

There are numerous problems arising especially from applications that have to do with various notions of flows in networks, for example:

- Max flow min cut theorem

## Visibility graph problems

- Museum guard problem

## Covering problems

Covering problems are specific instances of subgraph-finding problems, and they tend to be closely related to the clique problem or the independent set problem.

- Set cover problem
- Vertex cover problem

## Applications

Applications of graph theory are primarily, but not exclusively, concerned with labeled graphs and various specializations of these.

Structures that can be represented as graphs are ubiquitous, and many problems of practical interest can be represented by graphs. The link structure of a website could be represented by a directed graph: the vertices are the web pages available at the website and a directed edge from page  $A$  to page  $B$  exists if and only if  $A$  contains a link to  $B$ . A similar approach can be taken to problems in travel, biology, computer chip design, and many other fields. The development of algorithms to handle graphs is therefore of major interest in computer science. There, the transformation of graphs is often formalized and represented by graph rewrite systems. They are either directly used or properties of the rewrite systems (e.g. confluence) are studied.

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A graph structure can be extended by assigning a weight to each edge of the graph. Graphs with weights, or weighted graphs, are used to represent structures in which pairwise connections have some numerical values. For example if a graph represents a road network, the weights could represent the length of each road. A digraph with weighted edges in the context of graph theory is called a network.

Networks have many uses in the practical side of graph theory, network analysis (for example, to model and analyze traffic networks). Within network analysis, the definition of the term "network" varies, and may often refer to a simple graph.

Many applications of graph theory exist in the form of network analysis. These split broadly into three categories:

1. First, analysis to determine structural properties of a network, such as the distribution of vertex degrees and the diameter of the graph. A vast number of graph measures exist, and the production of useful ones for various domains remains an active area of research.
2. Second, analysis to find a measurable quantity within the network, for example, for a transportation network, the level of vehicular flow within any portion of it.
3. Third, analysis of dynamical properties of networks.

Graph theory is also used to study molecules in chemistry and physics. In condensed matter physics, the three dimensional structure of complicated simulated atomic structures can be studied quantitatively by gathering statistics on graph-theoretic properties related to the topology of the atoms. For example, Franzblau's shortest-path (SP) rings. In chemistry a graph makes a natural model for a molecule, where vertices represent atoms and edges bonds. This approach is especially used in computer processing of molecular structures, ranging from chemical editors to database searching.

Graph theory is also widely used in sociology as a way, for example, to measure actors' prestige or to explore diffusion mechanisms, notably through the use of social network analysis software.

Likewise, graph theory is useful in biology and conservation efforts where a vertex can represent regions where certain species exist (or habitats) and the edges represent migration paths, or movement between the regions. This information is important when looking at breeding patterns or tracking the spread of disease, parasites or how changes to the movement can affect other species.

## See also

- Gallery of named graphs
- Glossary of graph theory
- List of graph theory topics
- Publications in graph theory

## Related topics

- Graph property
  - Algebraic graph theory
  - Conceptual graph
  - Data structure
  - Disjoint-set data structure
  - Entitative graph
  - Existential graph
  - Graph data structure
  - Graph algebras
  - Graph automorphism
  - Graph coloring
-

- Graph database
- Graph drawing
- Graph equation
- Graph rewriting
- Logical graph
- Loop
- Null graph
- Quantum graph
- Spectral graph theory
- Strongly regular graphs
- Symmetric graphs
- Tree data structure

### **Algorithms**

- Bellman-Ford algorithm
- Dijkstra's algorithm
- Ford-Fulkerson algorithm
- Kruskal's algorithm
- Nearest neighbour algorithm
- Prim's algorithm
- Depth-first search
- Breadth-first search

### **Subareas**

- Algebraic graph theory
- Geometric graph theory
- Extremal graph theory
- Probabilistic graph theory
- Topological graph theory

### **Related areas of mathematics**

- Combinatorics
- Group theory
- Knot theory
- Ramsey theory

### **Generalizations**

- Hypergraph
  - Abstract simplicial complex
-

## Prominent graph theorists

- Berge, Claude
- Bollobás, Béla
- Chung, Fan
- Dirac, Gabriel Andrew
- Erdős, Paul
- Euler, Leonhard
- Faudree, Ralph
- Graham, Ronald
- Harary, Frank
- Heawood, Percy John
- Kőnig, Dénes
- Lovász, László
- Nešetřil, Jaroslav
- Rényi, Alfréd
- Ringel, Gerhard
- Robertson, Neil
- Seymour, Paul
- Szemerédi, Endre
- Thomas, Robin
- Thomassen, Carsten
- Turán, Pál
- Tutte, W. T.

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## External links

### Online textbooks

- Graph Theory with Applications <sup>[9]</sup> (1976) by Bondy and Murty
  - Phase Transitions in Combinatorial Optimization Problems, Section 3: Introduction to Graphs <sup>[10]</sup> (2006) by Hartmann and Weigt
  - Digraphs: Theory Algorithms and Applications <sup>[11]</sup> 2007 by Jorgen Bang-Jensen and Gregory Gutin
  - Graph Theory, by Reinhard Diestel <sup>[12]</sup>
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## Other resources

- Graph theory tutorial <sup>[13]</sup>
- Image gallery: graphs <sup>[14]</sup>
- Concise, annotated list of graph theory resources for researchers <sup>[15]</sup>

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# Algebraic topology

**Algebraic topology** is a branch of mathematics which uses tools from abstract algebra to study topological spaces. The basic goal is to find algebraic invariants that classify topological spaces up to homeomorphism. In many situations this is too much to hope for and it is more prudent to aim for a more modest goal, classification up to homotopy equivalence.

Although algebraic topology primarily uses algebra to study topological problems, the converse, using topology to solve algebraic problems, is sometimes also possible. Algebraic topology, for example, allows for a convenient proof that any subgroup of a free group is again a free group.

## The method of algebraic invariants

An older name for the subject was combinatorial topology, implying an emphasis on how a space  $X$  was constructed from simpler ones (the modern standard tool for such construction is the CW-complex). The basic method now applied in algebraic topology is to investigate spaces via algebraic invariants by mapping them, for example, to groups which have a great deal of manageable structure in a way that respects the relation of homeomorphism (or more general homotopy) of spaces. This allows one to recast statements about topological spaces into statements about groups, which are often easier to prove.

Two major ways in which this can be done are through fundamental groups, or more generally homotopy theory, and through homology and cohomology groups. The fundamental groups give us basic information about the structure of a topological space, but they are often nonabelian and can be difficult to work with. The fundamental group of a (finite) simplicial complex does have a finite presentation.

Homology and cohomology groups, on the other hand, are abelian and in many important cases finitely generated. Finitely generated abelian groups are completely classified and are particularly easy to work with.

## Setting in category theory

In general, all constructions of algebraic topology are functorial; the notions of category, functor and natural transformation originated here. Fundamental groups and homology and cohomology groups are not only *invariants* of the underlying topological space, in the sense that two topological spaces which are homeomorphic have the same associated groups, but their associated morphisms also correspond — a continuous mapping of spaces induces a group homomorphism on the associated groups, and these homomorphisms can be used to show non-existence (or, much more deeply, existence) of mappings.

## Results on homology

Several useful results follow immediately from working with finitely generated abelian groups. The free rank of the  $n$ -th homology group of a simplicial complex is equal to the  $n$ -th Betti number, so one can use the homology groups of a simplicial complex to calculate its Euler-Poincaré characteristic. As another example, the top-dimensional integral homology group of a closed manifold detects orientability: this group is isomorphic to either the integers or 0, according as the manifold is orientable or not. Thus, a great deal of topological information is encoded in the homology of a given topological space.

Beyond simplicial homology, which is defined only for simplicial complexes, one can use the differential structure of smooth manifolds via de Rham cohomology, or Čech or sheaf cohomology to investigate the solvability of differential equations defined on the manifold in question. De Rham showed that all of these approaches were interrelated and that, for a closed, oriented manifold, the Betti numbers derived through simplicial homology were the same Betti numbers as those derived through de Rham cohomology. This was extended in the 1950s, when Eilenberg and Steenrod generalized this approach. They defined homology and cohomology as functors equipped with natural transformations subject to certain axioms (e.g., a weak equivalence of spaces passes to an isomorphism of homology groups), verified that all existing (co)homology theories satisfied these axioms, and then proved that such an axiomatization uniquely characterized the theory.

A new approach uses a functor from filtered spaces to crossed complexes defined directly and homotopically using relative homotopy groups; a higher homotopy van Kampen theorem proved for this functor enables basic results in algebraic topology, especially on the border between homology and homotopy, to be obtained without using singular homology or simplicial approximation. This approach is also called non abelian algebraic topology, and generalises to higher dimensions ideas coming from the fundamental group.

## Applications of algebraic topology

Classic applications of algebraic topology include:

- The Brouwer fixed point theorem: every continuous map from the unit  $n$ -disk to itself has a fixed point.
- The  $n$ -sphere admits a nowhere-vanishing continuous unit vector field if and only if  $n$  is odd. (For  $n=2$ , this is sometimes called the "hairy ball theorem".)
- The Borsuk-Ulam theorem: any continuous map from the  $n$ -sphere to Euclidean  $n$ -space identifies at least one pair of antipodal points.
- Any subgroup of a free group is free. This result is quite interesting, because the statement is purely algebraic yet the simplest proof is topological. Namely, any free group  $G$  may be realized as the fundamental group of a graph  $X$ . The main theorem on covering spaces tells us that every subgroup  $H$  of  $G$  is the fundamental group of some covering space  $Y$  of  $X$ ; but every such  $Y$  is again a graph. Therefore its fundamental group  $H$  is free.
- Topological combinatorics

## Notable algebraic topologists

- Frank Adams
- Karol Borsuk
- Luitzen Egbertus Jan Brouwer
- William Browder
- Nicolas Bourbaki
- Henri Cartan
- Otto Hermann K nneth
- Samuel Eilenberg
- Peter Freyd
- Alexander Grothendieck
- Friedrich Hirzebruch
- Heinz Hopf
- Michael J. Hopkins
- Witold Hurewicz
- Egbert van Kampen
- Saunders Mac Lane
- Mark Mahowald
- J. Peter May
- John Coleman Moore
- Sergei Novikov
- Lev Pontryagin
- Daniel Quillen
- Jean-Pierre Serre
- Norman Steenrod
- Dennis Sullivan
- Ren  Thom
- Hassler Whitney
- J. H. C. Whitehead

## Important theorems in algebraic topology

- Borsuk-Ulam theorem
  - Brouwer fixed point theorem
  - Cellular approximation theorem
  - Eilenberg–Zilber theorem
  - Hurewicz theorem
  - K nneth theorem
  - Poincar  duality theorem
  - Universal coefficient theorem
  - Van Kampen's theorem
  - Generalized van Kampen's theorems<sup>[1]</sup>
  - Higher homotopy, generalized van Kampen's theorem<sup>[2]</sup>
  - Whitehead's theorem
-

## See also

- Important publications in algebraic topology
- GNUL Textbook on Algebraic Topology vol.1 <sup>[3]</sup><sup>[4]</sup>
- Higher dimensional algebra
- Higher category theory
- Van Kampen's theorem
- Groupoid
- Lie groupoid
- Lie algebroid
- Grothendieck topology
- Serre spectral sequence
- Sheaf
- Homotopy
- Homotopy theory
- Fundamental group
- Homology theory
- Homological algebra
- Cohomology theory
- K-theory
- Algebraic K-theory
- TQFT
- Homotopy quantum field theory (HQFT)
- CW complex
- Simplicial complex
- Homology complex
- Algebroid
- Exact sequence

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- Van Kampen's theorem <sup>[11]</sup> on PlanetMath
- Van Kampen's theorem result <sup>[12]</sup> on PlanetMath

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- Ronald Brown, Philip J. Higgins and Rafael Sivera. 2009. Higher dimensional, higher homotopy, generalized van Kampen Theorem., in *Nonabelian Algebraic Topology: filtered spaces, crossed complexes, cubical higher homotopy groupoids*. 512 pp, (Preprint). <sup>[10]</sup>
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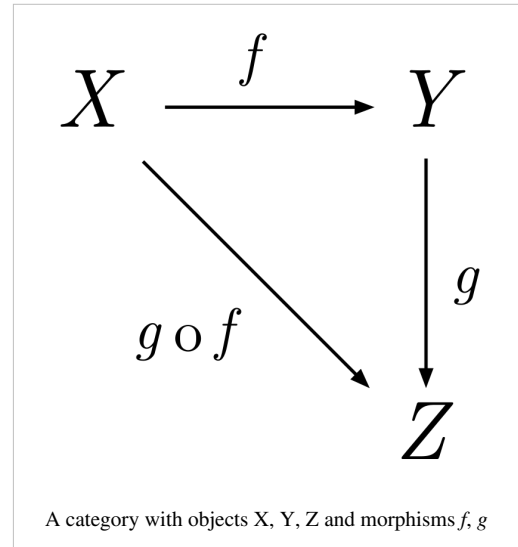
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- [13] <http://www.math.uchicago.edu/~may/VIGRE/VIGREREU2008.html>
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# Category theory

In mathematics, **category theory** deals in an abstract way with mathematical structures and relationships between them: it abstracts from *sets* and *functions* to *objects* linked in diagrams by *morphisms* or *arrows*.

One of the simplest examples of a category (which is a very important concept in topology) is that of groupoid, defined as a category whose arrows or morphisms are all invertible. Categories now appear in most branches of mathematics, some areas of theoretical computer science where they correspond to types, and mathematical physics where they can be used to describe vector spaces. Category theory provides both with a unifying notion and terminology. Categories were first introduced by Samuel Eilenberg and Saunders Mac Lane in 1942–45, in connection with algebraic topology.



Category theory has several faces known not just to specialists, but to other mathematicians. A term dating from the 1940s, "general abstract nonsense", refers to its high level of abstraction, compared to more classical branches of mathematics. Homological algebra is category theory in its aspect of organising and suggesting manipulations in abstract algebra. Diagram chasing is a visual method of arguing with abstract "arrows" joined in diagrams. Note that arrows between categories are called functors, subject to specific defining commutativity conditions; moreover, categorical diagrams and sequences can be defined as functors (viz. Mitchell, 1965). An arrow between two functors is a natural transformation when it is subject to certain naturality or commutativity conditions. Both functors and natural transformations are key concepts in category theory, or the "real engines" of category theory. To paraphrase a famous sentence of the mathematicians who founded category theory: 'Categories were introduced to define functors, and functors were introduced to define natural transformations'. Topos theory is a form of abstract sheaf theory, with geometric origins, and leads to ideas such as pointless topology. A topos can also be considered as a specific type of category with two additional topos axioms.

## Background

The study of categories is an attempt to *axiomatically* capture what is commonly found in various classes of related *mathematical structures* by relating them to the *structure-preserving functions* between them. A systematic study of category theory then allows us to prove general results about any of these types of mathematical structures from the axioms of a category.

Consider the following example. The class **Grp** of groups consists of all objects having a "group structure". One can proceed to prove theorems about groups by making logical deductions from the set of axioms. For example, it is immediately proved from the axioms that the identity element of a group is unique.

Instead of focusing merely on the individual objects (e.g., groups) possessing a given structure, category theory emphasizes the morphisms – the structure-preserving mappings – *between* these objects; by studying these morphisms, we are able to learn more about the structure of the objects. In the case of groups, the morphisms are the group homomorphisms. A group homomorphism between two groups "preserves the group structure" in a precise sense – it is a "process" taking one group to another, in a way that carries along information about the structure of the first group into the second group. The study of group homomorphisms then provides a tool for studying general properties of groups and consequences of the group axioms.

A similar type of investigation occurs in many mathematical theories, such as the study of continuous maps (morphisms) between topological spaces in topology (the associated category is called **Top**), and the study of smooth functions (morphisms) in manifold theory.

If one axiomatizes relations instead of functions, one obtains the theory of allegories.

## Functors

Abstracting again, a category is *itself* a type of mathematical structure, so we can look for "processes" which preserve this structure in some sense; such a process is called a functor. A functor associates to every object of one category an object of another category, and to every morphism in the first category a morphism in the second.

In fact, what we have done is define a category of *categories and functors* – the objects are categories, and the morphisms (between categories) are functors.

By studying categories and functors, we are not just studying a class of mathematical structures and the morphisms between them; we are studying the *relationships between various classes of mathematical structures*. This is a fundamental idea, which first surfaced in algebraic topology. Difficult *topological* questions can be translated into *algebraic* questions which are often easier to solve. Basic constructions, such as the fundamental group or fundamental groupoid <sup>[1]</sup> of a topological space, can be expressed as fundamental functors <sup>[1]</sup> to the category of groupoids in this way, and the concept is pervasive in algebra and its applications.

## Natural transformation

Abstracting yet again, constructions are often "naturally related" – a vague notion, at first sight. This leads to the clarifying concept of natural transformation, a way to "map" one functor to another. Many important constructions in mathematics can be studied in this context. "Naturality" is a principle, like general covariance in physics, that cuts deeper than is initially apparent.

## Historical notes

In 1942–45, Samuel Eilenberg and Saunders Mac Lane introduced categories, functors, and natural transformations as part of their work in topology, especially algebraic topology. Their work was an important part of the transition from intuitive and geometric homology to axiomatic homology theory. Eilenberg and Mac Lane later wrote that their goal was to understand natural transformations; in order to do that, functors had to be defined, which required categories.

Stanislaw Ulam, and some writing on his behalf, have claimed that related ideas were current in the late 1930s in Poland. Eilenberg was Polish, and studied mathematics in Poland in the 1930s. Category theory is also, in some sense, a continuation of the work of Emmy Noether (one of Mac Lane's teachers) in formalizing abstract processes; Noether realized that in order to understand a type of mathematical structure, one needs to understand the processes preserving that structure. In order to achieve this understanding, Eilenberg and Mac Lane proposed an axiomatic formalization of the relation between structures and the processes preserving them.

The subsequent development of category theory was powered first by the computational needs of homological algebra, and later by the axiomatic needs of algebraic geometry, the field most resistant to being grounded in either axiomatic set theory or the Russell-Whitehead view of united foundations. General category theory, an extension of universal algebra having many new features allowing for semantic flexibility and higher-order logic, came later; it is now applied throughout mathematics.

Certain categories called topoi (singular *topos*) can even serve as an alternative to axiomatic set theory as a foundation of mathematics. These foundational applications of category theory have been worked out in fair detail as a basis for, and justification of, constructive mathematics. More recent efforts to introduce undergraduates to categories as a foundation for mathematics include Lawvere and Rosebrugh (2003) and Lawvere and Schanuel

(1997).

Categorical logic is now a well-defined field based on type theory for intuitionistic logics, with applications in functional programming and domain theory, where a cartesian closed category is taken as a non-syntactic description of a lambda calculus. At the very least, category theoretic language clarifies what exactly these related areas have in common (in some abstract sense).

## Categories, objects, and morphisms

A category  $C$  consists of the following three mathematical entities:

- A class  $\text{ob}(C)$ , whose elements are called *objects*;
- A class  $\text{hom}(C)$ , whose elements are called morphisms or maps or *arrows*. Each morphism  $f$  has a unique *source object*  $a$  and *target object*  $b$ . We write  $f: a \rightarrow b$ , and we say " $f$  is a morphism from  $a$  to  $b$ ". We write  $\text{hom}(a, b)$  (or  $\text{Hom}(a, b)$ , or  $\text{hom}_C(a, b)$ , or  $\text{Mor}(a, b)$ , or  $C(a, b)$ ) to denote the *hom-class* of all morphisms from  $a$  to  $b$ .
- A binary operation  $\circ$ , called *composition of morphisms*, such that for any three objects  $a, b$ , and  $c$ , we have  $\text{hom}(a, b) \times \text{hom}(b, c) \rightarrow \text{hom}(a, c)$ . The composition of  $f: a \rightarrow b$  and  $g: b \rightarrow c$  is written as  $g \circ f$  or  $gf$ <sup>[2]</sup>, governed by two axioms:
  - Associativity: If  $f: a \rightarrow b$ ,  $g: b \rightarrow c$  and  $h: c \rightarrow d$  then  $h \circ (g \circ f) = (h \circ g) \circ f$ , and
  - Identity: For every object  $x$ , there exists a morphism  $1_x: x \rightarrow x$  called the *identity morphism* for  $x$ , such that for every morphism  $f: a \rightarrow b$ , we have  $1_b \circ f = f = f \circ 1_a$ .

From these axioms, it can be proved that there is exactly one identity morphism for every object. Some authors deviate from the definition just given by identifying each object with its identity morphism.

Relations among morphisms (such as  $fg = h$ ) are often depicted using commutative diagrams, with "points" (corners) representing objects and "arrows" representing morphisms.

## Properties of morphisms

Some morphisms have important properties. A morphism  $f: a \rightarrow b$  is:

- a monomorphism (or *monic*) if  $fg_1 = fg_2$  implies  $g_1 = g_2$  for all morphisms  $g_1, g_2: x \rightarrow a$ .
- an epimorphism (or *epic*) if  $g_1f = g_2f$  implies  $g_1 = g_2$  for all morphisms  $g_1, g_2: b \rightarrow x$ .
- an isomorphism if there exists a morphism  $g: b \rightarrow a$  with  $fg = 1_b$  and  $gf = 1_a$ .<sup>[3]</sup>
- an endomorphism if  $a = b$ .  $\text{end}(a)$  denotes the class of endomorphisms of  $a$ .
- an automorphism if  $f$  is both an endomorphism and an isomorphism.  $\text{aut}(a)$  denotes the class of automorphisms of  $a$ .

## Functors

Functors are structure-preserving maps between categories. They can be thought of as morphisms in the category of all (small) categories.

A (**covariant**) functor  $F$  from a category  $C$  to a category  $D$ , written  $F: C \rightarrow D$ , consists of:

- for each object  $x$  in  $C$ , an object  $F(x)$  in  $D$ ; and
- for each morphism  $f: x \rightarrow y$  in  $C$ , a morphism  $F(f): F(x) \rightarrow F(y)$ ,

such that the following two properties hold:

- For every object  $x$  in  $C$ ,  $F(1_x) = 1_{F(x)}$ ;
- For all morphisms  $f: x \rightarrow y$  and  $g: y \rightarrow z$ ,  $F(g \circ f) = F(g) \circ F(f)$ .

A **contravariant** functor  $F: C \rightarrow D$ , is like a covariant functor, except that it "turns morphisms around" ("reverses all the arrows"). More specifically, every morphism  $f: x \rightarrow y$  in  $C$  must be assigned to a morphism  $F(f): F(y) \rightarrow F(x)$  in  $D$ . In other words, a contravariant functor is a covariant functor from the opposite category  $C^{\text{op}}$  to  $D$ .



## Natural transformations and isomorphisms

A *natural transformation* is a relation between two functors. Functors often describe "natural constructions" and natural transformations then describe "natural homomorphisms" between two such constructions. Sometimes two quite different constructions yield "the same" result; this is expressed by a natural isomorphism between the two functors.

If  $F$  and  $G$  are (covariant) functors between the categories  $C$  and  $D$ , then a natural transformation from  $F$  to  $G$  associates to every object  $x$  in  $C$  a morphism  $\eta_x : F(x) \rightarrow G(x)$  in  $D$  such that for every morphism  $f : x \rightarrow y$  in  $C$ , we have  $\eta_y \circ F(f) = G(f) \circ \eta_x$ ; this means that the following diagram is commutative:

$$\begin{array}{ccc} F(X) & \xrightarrow{F(f)} & F(Y) \\ \eta_X \downarrow & & \downarrow \eta_Y \\ G(X) & \xrightarrow{G(f)} & G(Y) \end{array}$$

The two functors  $F$  and  $G$  are called *naturally isomorphic* if there exists a natural transformation from  $F$  to  $G$  such that  $\eta_x$  is an isomorphism for every object  $x$  in  $C$ .

## Universal constructions, limits, and colimits

Using the language of category theory, many areas of mathematical study can be cast into appropriate categories, such as the categories of all sets, groups, topologies, and so on. These categories surely have some objects that are "special" in a certain way, such as the empty set or the product of two topologies, yet in the definition of a category, objects are considered to be atomic, i.e., we *do not know* whether an object  $A$  is a set, a topology, or any other abstract concept – hence, the challenge is to define special objects without referring to the internal structure of those objects. But how can we define the empty set without referring to elements, or the product topology without referring to open sets?

The solution is to characterize these objects in terms of their relations to other objects, as given by the morphisms of the respective categories. Thus, the task is to find *universal properties* that uniquely determine the objects of interest. Indeed, it turns out that numerous important constructions can be described in a purely categorical way. The central concept which is needed for this purpose is called categorical *limit*, and can be dualized to yield the notion of a *colimit*.

## Equivalent categories

It is a natural question to ask: under which conditions can two categories be considered to be "essentially the same", in the sense that theorems about one category can readily be transformed into theorems about the other category? The major tool one employs to describe such a situation is called *equivalence of categories*, which is given by appropriate functors between two categories. Categorical equivalence has found numerous applications in mathematics.

## Further concepts and results

The definitions of categories and functors provide only the very basics of categorical algebra; additional important topics are listed below. Although there are strong interrelations between all of these topics, the given order can be considered as a guideline for further reading.

- The functor category  $D^C$  has as objects the functors from  $C$  to  $D$  and as morphisms the natural transformations of such functors. The Yoneda lemma is one of the most famous basic results of category theory; it describes representable functors in functor categories.
- Duality: Every statement, theorem, or definition in category theory has a *dual* which is essentially obtained by "reversing all the arrows". If one statement is true in a category  $C$  then its dual will be true in the dual category  $C^{\text{op}}$ . This duality, which is transparent at the level of category theory, is often obscured in applications and can lead to surprising relationships.
- Adjoint functors: A functor can be left (or right) adjoint to another functor that maps in the opposite direction. Such a pair of adjoint functors typically arises from a construction defined by a universal property; this can be seen as a more abstract and powerful view on universal properties.

## Higher-dimensional categories

Many of the above concepts, especially equivalence of categories, adjoint functor pairs, and functor categories, can be situated into the context of *higher-dimensional categories*. Briefly, if we consider a morphism between two objects as a "process taking us from one object to another", then higher-dimensional categories allow us to profitably generalize this by considering "higher-dimensional processes".

For example, a (strict) 2-category is a category together with "morphisms between morphisms", i.e., processes which allow us to transform one morphism into another. We can then "compose" these "bimorphisms" both horizontally and vertically, and we require a 2-dimensional "exchange law" to hold, relating the two composition laws. In this context, the standard example is **Cat**, the 2-category of all (small) categories, and in this example, bimorphisms of morphisms are simply natural transformations of morphisms in the usual sense. Another basic example is to consider a 2-category with a single object; these are essentially monoidal categories. Bicategories are a weaker notion of 2-dimensional categories in which the composition of morphisms is not strictly associative, but only associative "up to" an isomorphism.

This process can be extended for all natural numbers  $n$ , and these are called  $n$ -categories. There is even a notion of  $\omega$ -category corresponding to the ordinal number  $\omega$ .

Higher-dimensional categories are part of the broader mathematical field of higher-dimensional algebra, a concept introduced by Ronald Brown. For a conversational introduction to these ideas, see John Baez, 'A Tale of  $n$ -categories' (1996).<sup>[4]</sup>

## See also

- Domain theory
- Enriched category theory
- Glossary of category theory
- Higher category theory
- Higher-dimensional algebra
- Important publications in category theory
- Timeline of category theory and related mathematics

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## External links

- Chris Hillman, Categorical primer <sup>[14]</sup>, formal introduction to Category Theory.
- J. Adamek, H. Herrlich, G. Stecker, Abstract and Concrete Categories-The Joy of Cats <sup>[15]</sup>
- Stanford Encyclopedia of Philosophy: "Category Theory <sup>[16]</sup>" -- by Jean-Pierre Marquis. Extensive bibliography.
- Homepage of the Categories mailing list, <sup>[17]</sup> with extensive resource list.
- Baez, John, 1996, "The Tale of  $n$ -categories. <sup>[4]</sup>" An informal introduction to higher order categories.
- The catsters <sup>[18]</sup> a Youtube channel about category theory.
- Category Theory <sup>[19]</sup> on PlanetMath
- Categories, Logic and the Foundations of Physics <sup>[20]</sup>, Webpage dedicated to the use of Categories and Logic in the Foundations of Physics.
- Interactive Web page <sup>[21]</sup> which generates examples of categorical constructions in the category of finite sets.  
Written by Jocelyn Paine <sup>[22]</sup>

## References

- [1] <http://planetphysics.org/encyclopedia/FundamentalGroupoidFunctor.html>
- [2] Some authors compose in the opposite order, writing  $fg$  or  $f \circ g$  for  $g \circ f$ . Computer scientists using category theory very commonly write  $f;g$  for  $g \circ f$
- [3] Note that a morphism that is both epic and monic is not necessarily an isomorphism! For example, in the category consisting of two objects  $A$  and  $B$ , the identity morphisms, and a single morphism  $f$  from  $A$  to  $B$ ,  $f$  is both epic and monic but is not an isomorphism.
- [4] <http://math.ucr.edu/home/baez/week73.html>
- [5] <http://katmat.math.uni-bremen.de/acc/acc.htm>
- [6] <http://folli.loria.fr/cds/1999/library/pdf/barrwells.pdf>
- [7] <http://www.cwru.edu/artsci/math/wells/pub/ttt.html>
- [8] <http://www.tac.mta.ca/tac/reprints/articles/3/tr3abs.html>
- [9] <http://dlxs2.library.cornell.edu/cgi/t/text/text-idx?c=math;cc=math;view=toc;subview=short;idno=Gold010>
- [10] <http://www.maths.gla.ac.uk/~tl/book.html>
- [11] <http://citeseer.ist.psu.edu/martini96element.html>
- [12] <http://www.cs.man.ac.uk/~hsimmons/BOOKS/CatTheory.pdf>
- [13] <http://www.dcs.ed.ac.uk/home/dt/CT/categories.pdf>
- [14] <http://citeseer.ist.psu.edu/cache/papers/cs/23543/http:zSzzSzwww-aix.gsi.dezSz~appelzSzskripteSzotherzSzcategories.pdf/hillman01categorical.pdf>
- [15] <http://katmat.math.uni-bremen.de/acc/acc.pdf>
- [16] <http://plato.stanford.edu/entries/category-theory/>
- [17] <http://www.mta.ca/~cat-dist/categories.html>
- [18] <http://www.youtube.com/user/TheCatsters>
- [19] <http://planetmath.org/?op=getobj&from=objects&id=5622>
- [20] <http://categorieslogicphysics.wikidot.com/>
- [21] <http://www.j-paine.org/cgi-bin/webcats/webcats.php>
- [22] <http://www.j-paine.org/>

# Symbolic logic

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**Symbolic logic** is the area of mathematics which studies the purely formal properties of strings of symbols. The interest in this area springs from two sources. First, the symbols used in symbolic logic can be seen as representing the words used in philosophical logic. Second, the rules for manipulating symbols found in symbolic logic can be implemented on a computing machine.

Symbolic logic is usually divided into two subfields, propositional logic and predicate logic. Other logics of interest include temporal logic, modal logic and fuzzy logic. See also model theory.

Modern mathematical areas arising out of formal logic are grouped under the heading mathematical logic.

## Propositional logic

The area of symbolic logic called propositional logic, originally called *propositional calculus* but not to be confused with the branch of mathematics calculus, studies the properties of sentences formed from constants, usually designated  $p, q, r, \dots$  and five logical operators, AND, OR, IF...THEN, IF AND ONLY IF and NOT. The corresponding logical operations are known, respectively, as conjunction, disjunction, material conditional, biconditional, and negation. These five operators are sometimes denoted as keywords, especially in computer languages, and sometimes by special symbols (see Table of logic symbols). All except NOT are binary operators; NOT is a unary operator which precedes its operand. The values of these operators are given by truth tables. It is to be noted that capital letters are usually used to represent propositions groups in metalanguage. For example,  $A \ \& \ B$  is a metalinguistic way of conjoining either individual or grouped propositions.  $A \ \& \ B$  could represent  $p \ \& \ q$ , but it could also very well represent  $(p \ \& \ Q \ \& \ [\text{NOT}]r) \ \& \ (p \ \& \ r)$ . Syntactic rules will always be formulated in metalanguage.

The Sheffer operator, which parallels the *nand* operator in computer language, is also used to mark logical incompatibility or binary inconsistency. The neither...nor operator is also commonplace, as well as the exclusive disjunction. The sheffer operator is commonly represented as  $|$ , while the exclusive *Or* and the neither...nor operators are represented by the  $w$  sign and a downwards arrow respectively.

All complex connectors (conditional, biconditional, sheffer, neither...nor) can be reduced to the three fundamental connectors which are the conjunction, disjunction and negation (Not). For example, the exclusive disjunction can be symbolized as an inclusive disjunction conjoined with the negation of the conjoint elements. Formally, this gives:

$(p \text{ [exclusive OR] } q)$  is equivalent to  $( [ p \text{ [inclusive OR] } q] \ \& \ [\text{NOT} (p \ \& \ q)] )$

It would seem that this aspect of symbolic logic is what makes it more enlightening concerning the basic operations of the mind than the old Aristotelian logical axioms; modus ponens and syllogism can in fact be represented more fundamentally by the properties of the three basic connectors of symbolic logic. The material conditional, which operates the link between premisses and conclusions in syllogisms, is reducible to more basic operations and is in fact a composite of the mind's basic operations, a synthesis appearing intuitively elementary and fundamental.

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## Predicate logic

Predicate logic, originally called *predicate calculus*, expands on propositional logic by the introduction of variables, usually denoted by  $x, y, z$ , or other lowercase letters, and also by the introduction of sentences containing variables, called predicates, usually denoted by an uppercase letter followed by a list of variables, such as  $P(x)$  or  $Q(y,z)$ . In addition, predicate logic allows so-called quantifiers, representing ALL and EXISTS.

## Trivia

Symbolic logic is used to *prove* the seemingly simple statement " $1+1=2$ ". However, the proof is far from trivial and is in fact 360 pages long. Mathematicians Alfred North Whitehead and Bertrand Russell did so in their book *Principia Mathematica*.

## See also

- Substitution (logic)
- Table of logic symbols

# Relation algebra

In mathematics and abstract algebra, a **relation algebra** is a residuated Boolean algebra equipped with an involution called "converse". The motivating example of a relation algebra is the algebra  $2^{X^2}$  of all binary relations on a set  $X$ , with  $R \bullet S$  interpreted as the usual composition of binary relations and the converse of  $R$  as the inverse relation. Relation algebra emerged in the 19th century work of Augustus De Morgan and Charles Peirce, which culminated in the algebraic logic of Ernst Schröder. The present-day purely equational form of relation algebra was developed by Alfred Tarski and his students, starting in the 1940s.

## Definition

A **relation algebra**  $(L, \wedge, \vee, \neg, 0, 1, \bullet, \mathbf{I}, \square, \sqsupset, \smile)$  is an algebraic structure such that

- $(L, \wedge, \vee, \bullet, \mathbf{I}, \square, \sqsupset)$  is a residuated Boolean algebra, and
- the unary operation  $x \smile$  satisfies  $x \smile \square \mathbf{I} = x = \mathbf{I} \square x \smile$ .

Since  $x \square y$  can be defined in terms of composition and converse as  $x \smile \bullet y$ , and dually  $x \sqsupset y$  as  $x \bullet y \smile$ , it is not necessary to include  $\square$  or  $\sqsupset$  in the signature, which can therefore be simplified to  $(L, \wedge, \vee, \neg, 0, 1, \bullet, \mathbf{I}, \smile)$ , the more usual form of the signature for relation algebras. On the other hand  $x \smile$  is definable as either  $x \square \mathbf{I}$  or  $\mathbf{I} \square x$ , in which case a relation algebra can have the same signature as a residuated Boolean algebra. With that definition the axioms become  $(x \square \mathbf{I}) \square \mathbf{I} = x = \mathbf{I} \square (\mathbf{I} \square x)$ . But this simply asserts that  $\square \mathbf{I}$  and  $\mathbf{I} \square$  are involutions. Jónsson and Tsinakis have shown that if either one is an involution then so is the other and they are then the same operation, namely converse. This leads to a particularly straightforward definition:

*A relation algebra is a residuated Boolean algebra  $(L, \wedge, \vee, \neg, 0, 1, \bullet, \mathbf{I}, \square, \sqsupset)$  such that  $\mathbf{I} \square$  is an involution.*

When  $x \square y$  is viewed as a form of quotient of  $x$  by  $y$ , with  $\mathbf{I}$  as the corresponding multiplicative unit,  $x \smile = \mathbf{I} \square x$  can be understood as the *reciprocal* of  $x$  by syntactic analogy with  $1/x$ , a term some authors use synonymously with converse.

Since residuated Boolean algebras are axiomatized with finitely many equations, so are relation algebras, which therefore form a finitely axiomatized variety called **RA**, the variety of relation algebras.

## Axioms

The axioms **B1-B10** below are adapted from Givant (2006: 283), and were first set out by Tarski in 1948.<sup>[1]</sup> This axiomatization is predicated on a relation algebra being an algebraic structure over some Cartesian square  $L$ , having signature  $\langle L, \vee, \bullet, ^-, \smile, \mathbf{I} \rangle$  of type  $\langle 2, 2, 1, 1, 0 \rangle$ .

$L$  is a Boolean algebra under binary disjunction,  $\vee$ , and unary complementation  $()^-$ :

$$\mathbf{B1}: A \vee B = B \vee A$$

$$\mathbf{B2}: A \vee (B \vee C) = (A \vee B) \vee C$$

$$\mathbf{B3}: (A^- \vee B)^- \vee (A^- \vee B^-)^- = A$$

This axiomatization of Boolean algebra is due to Huntington (1933).

$L$  is a monoid under binary composition  $(\bullet)$  and nullary identity  $\mathbf{I}$ :

$$\mathbf{B4}: A \bullet (B \bullet C) = (A \bullet B) \bullet C$$

$$\mathbf{B5}: A \bullet \mathbf{I} = A$$

Unary converse  $()^\smile$  is an involution with respect to composition:

$$\mathbf{B6}: A^\smile^\smile = A$$

$$\mathbf{B7}: (A \bullet B)^\smile = B^\smile \bullet A^\smile$$

Converse and composition distribute over disjunction:

$$\mathbf{B8}: (A \vee B)^\smile = A^\smile \vee B^\smile$$

$$\mathbf{B9}: (A \vee B) \bullet C = (A \bullet C) \vee (B \bullet C)$$

**B10** is Tarski's equational form of the fact, discovered by Augustus De Morgan, that  $A \bullet B \leq C^- \leftrightarrow A^\smile \bullet C \leq B^- \leftrightarrow C \bullet B^\smile \leq A^-$ .

$$\mathbf{B10}: (A^\smile \bullet (A \bullet B)^-) \vee B^- = B^-$$

These axioms are ZFC theorems; for the purely Boolean **B1-B3**, this fact is trivial. After each of the following axioms is shown the number of the corresponding theorem in chpt. 3 of Suppes (1960), an exposition of ZFC: **B4** 27, **B5** 45, **B6** 14, **B7** 26, **B8** 16, **B9** 23.

## Expressing properties of binary relations in RA

The following table shows how many of the usual properties of binary relations can be expressed as succinct inequalities or equalities using **RA** operations. Below, an inequality of the form  $A \leq B$  is shorthand for a Boolean equation of the form  $A \vee B = B$ .

The most complete set of results of this nature is chpt. C of Carnap (1958), where the notation is rather distant from those of this entry. Chpt. 3.2 of Suppes (1960) contains fewer results, but they are presented as ZFC theorems, using a notation that more resembles that of this entry. Neither Carnap nor Suppes formulate their results using the **RA** of this entry, or in an equational manner.

| $R$ is                               | If and only if:                                                                     |
|--------------------------------------|-------------------------------------------------------------------------------------|
| Surjective                           | $R \circ R \leq I$                                                                  |
| Injective<br>( $R \circ$ surjective) | $R \bullet R \leq I$                                                                |
| 1-to-1                               | $R$ is surjective and injective.                                                    |
| Total or<br>Connected                | $I \leq R \vee R \circ$                                                             |
| Functional                           |                                                                                     |
| Function                             | $R$ is functional and total.                                                        |
| 1-1 Function                         | $R \circ R = I$ and $R \bullet R \leq I$ . $R$ is total, functional, and injective. |
| Reflexive                            | $I \leq R$                                                                          |
| Irreflexive                          | $R \wedge I = 0$ . ( $0 = I^\neg$ )                                                 |
| Transitive                           | $R \bullet R \leq R$                                                                |
| Preorder                             | $R$ is reflexive and transitive.                                                    |
| Antisymmetric                        | $R \wedge R \circ \leq I$                                                           |
| Partial order                        | $R$ is an antisymmetric preorder.                                                   |
| Total order                          | $R$ is a total partial order.                                                       |
| Strict partial order                 | $R$ is transitive and irreflexive.                                                  |
| Strict total order                   | $R$ is a total strict partial order.                                                |
| Symmetric                            | $R = R \circ$                                                                       |
| Equivalence                          | $R \bullet R \circ = R$ . $R$ is a symmetric preorder.                              |
| Asymmetric                           | $R \neq R \circ$                                                                    |
| Dense                                | $R \wedge 0 \leq (R \wedge 0) \bullet (R \wedge 0)$ .                               |

## Expressive power

The metamathematics of **RA** are discussed at length in Tarski and Givant (1987), and more briefly in Givant (2006).

**RA** consists entirely of equations manipulated using nothing more than uniform replacement and the substitution of equals for equals. Both rules are wholly familiar from school mathematics and from abstract algebra generally. Hence **RA** proofs are carried out in a manner familiar to all mathematicians, unlike the case in mathematical logic generally.

**RA** can express any (and up to logical equivalence, exactly the) first-order logic (FOL) formulas containing no more than three variables. (A given variable can be quantified multiple times as long as the quantifiers do not nest more than 3 deep.) Surprisingly, this fragment of FOL suffices to express Peano arithmetic and almost all axiomatic set theories ever proposed. Hence **RA** is, in effect, a way of algebraizing nearly all mathematics, while dispensing with FOL and its connectives, quantifiers, turnstiles, and modus ponens. Because **RA** can express Peano arithmetic and set theory, Gödel's incompleteness theorems apply to it; **RA** is incomplete, incompletable, and undecidable. (N.B. The Boolean algebra fragment of **RA** is complete and decidable.)

The **representable relation algebras**, forming the class **RRA**, are those relation algebras isomorphic to some relation algebra consisting of binary relations on some set, and closed under the standard interpretations of the **RA**



operations. It is easily shown, e.g. using the method of pseudoelementary classes, that **RRA** is a quasivariety, that is, axiomatizable by a universal Horn theory. In 1950, Roger Lyndon proved the existence of equations holding in **RRA** that did not hold in **RA**, that is, the variety generated by **RRA** is a proper subvariety of the variety **RA**. In 1955, Alfred Tarski showed that **RRA** is itself a variety, which however, as shown by Donald Monk in 1964, has no finite axiomatization, unlike **RA** which is finitely axiomatized by definition. That not every relation algebra is representable is a fundamental way relation algebras differ from Boolean algebras, which are always representable as sets of subsets of some set closed under union, intersection, and complement.

## Examples

1. Any Boolean algebra can be turned into a relation algebra by interpreting conjunction as composition (the monoid multiplication  $\bullet$ ), i.e.  $x \bullet y$  is defined as  $x \wedge y$ . This interpretation requires that converse interpret identity ( $\check{y} = y$ ), and that both residuals  $y \backslash x$  and  $x / y$  interpret the conditional  $y \rightarrow x$  (i.e.,  $\neg y \vee x$ ).
2. The motivating example of a relation algebra depends on the definition of a binary relation  $R$  on a set  $X$  as any subset  $R \subseteq X^2$ . The power set  $2^{X^2}$  consisting of all binary relations on  $X$  is a Boolean algebra. While  $2^{X^2}$  can be made a relation algebra by taking  $R \bullet S = R \wedge S$  as for the preceding example, the standard interpretation of  $\bullet$  is instead given by  $x(R \bullet S)z = \exists y. xRySz$ . That is, the pair  $(x, z)$  belongs to the relation  $R \bullet S$  just when there exists  $y \in X$  such that  $(x, y) \in R$  and  $(y, z) \in S$ . This interpretation uniquely determines  $R \backslash S$  to consist of all pairs  $(y, z)$  such that for all  $x \in X$ , if  $xRy$  then  $xSz$ . Dually  $S / R$  consists of all pairs  $(x, y)$  such that for all  $z \in X$ , if  $yRz$  then  $xSz$ . The translation  $\check{y} = \neg(y \backslash \mathbf{I})$  then establishes the converse  $R \smile$  of  $R$  as consisting of all pairs  $(y, x)$  such that  $(x, y) \in R$ .
3. An important generalization of the previous example is the power set  $2^E$  where  $E \subseteq X^2$  is any equivalence relation on the set  $X$ . This is a generalization because  $X^2$  is itself an equivalence relation, namely the complete relation consisting of all pairs. While  $2^E$  is not a subalgebra of  $2^{X^2}$  when  $E \neq X^2$  (since in that case it does not contain the relation  $X^2$ , the top element  $1$  being  $E$  instead of  $X^2$ ), it is nevertheless made a relation algebra using the same definitions of the operations. Its importance resides in the definition of a *representable relation algebra* as any relation algebra isomorphic to a subalgebra of the relation algebra  $2^E$  for some equivalence relation  $E$  on some set. Refer to the previous section for more on the relevant metamathematics.
4. If group sum or product interprets composition, group inverse interprets converse, group identity interprets  $\mathbf{I}$ , and if  $R$  is a one to one correspondence, so that  $R \smile \bullet R = R \bullet R \smile = \mathbf{I}$ ,<sup>[2]</sup> then  $L$  is a group as well as a monoid. **B4-B7** become well-known theorems of group theory, so that relation algebra becomes a proper extension of group theory as well as of Boolean algebra, a fact indicative of its great expressive power.

## Historical remarks

DeMorgan founded **RA** in 1860, but C. S. Peirce took it much further and became fascinated with its philosophical power. The work of DeMorgan and Peirce came to be known mainly in the extended and definitive form Ernst Schröder gave it in Vol. 3 of his *Vorlesungen* (1890-1905). *Principia Mathematica* drew strongly on Schröder's **RA**, but acknowledged him only as the inventor of the notation. In 1912, Alwin Korselt proved that a particular formula in which the quantifiers were nested 4 deep had no **RA** equivalent.<sup>[3]</sup> This fact led to a loss of interest in **RA** until Tarski (1941) began writing about it. His students have continued to develop **RA** down to the present day. Tarski returned to **RA** in the 1970s with the help of Steven Givant; this collaboration resulted in the monograph Tarski and Givant (1987), the definitive reference for this subject. For more on the history of **RA**, see Maddux (1991, 2006).

## Software

- RelMICS / Relational Methods in Computer Science <sup>[4]</sup> maintained by Wolfram Kahl <sup>[5]</sup>
- Carsten Sinz: ARA / An Automatic Theorem Prover for Relation Algebras <sup>[6]</sup>

## See also

- |                              |                         |                                 |
|------------------------------|-------------------------|---------------------------------|
| • Algebraic logic            | • Cylindric algebras    | • Relational calculus           |
| • Allegory (category theory) | • Extension in logic    | • Relational algebra            |
| • Binary relation            | • Involution            | • Relative product of relations |
| • Cartesian product          | • Logic of relatives    | • Residuated Boolean algebra    |
| • Cartesian square           | • Relation              | • Spatial-temporal reasoning    |
| • Composition of relations   | • Relation construction | • Theory of relations           |
| • Converse of a relation     | • Relation reduction    | • Triadic relation              |

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## External links

- Yohji AKAMA, Yasuo Kawahara, and Hitoshi Furusawa, "Constructing Allegory from Relation Algebra and Representation Theorems." <sup>[8]</sup>
- Richard Bird, Oege de Moor, Paul Hoogendijk, "Generic Programming with Relations and Functors." <sup>[9]</sup>
- R.P. de Freitas and Viana, "A Completeness Result for Relation Algebra with Binders." <sup>[10]</sup>
- Peter Jipsen <sup>[11]</sup>:
  - Relation algebras <sup>[12]</sup>. In Mathematical structures. <sup>[13]</sup> If there are problems with LaTeX, see an old HTML version here. <sup>[14]</sup>
  - "Foundations of Relations and Kleene Algebra." <sup>[15]</sup>
  - "Computer Aided Investigations of Relation Algebras." <sup>[16]</sup>
  - "A Gentzen System And Decidability For Residuated Lattices." <sup>[17]</sup>
- Vaughan Pratt:

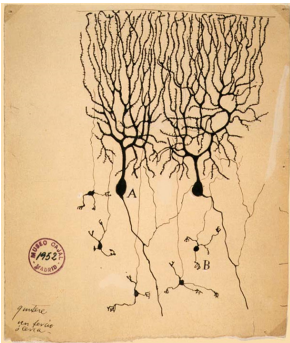
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# Neuron

Neuron: neuron (Nerve Cell)



Drawing by Santiago Ramón y Cajal of neurons in the pigeon cerebellum. (A) Denotes Purkinje cells, an example of a multipolar neuron. (B) Denotes granule cells which are also multipolar.

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A **neuron** (pronounced /ˈnjʊərɒn/ *N(Y)OOR-on*, also known as a **neurone** or **nerve cell**) is an electrically excitable cell that processes and transmits information by electrochemical signaling, via connections with other cells called synapses. Neurons are the core components of the nervous system, which includes the brain, spinal cord, and peripheral ganglia. A number of specialized types of neurons exist: sensory neurons respond to touch, sound, light and numerous other stimuli affecting cells of the sensory organs that then send signals to the spinal cord and brain. Motor neurons receive signals from the brain and spinal cord and cause muscle contractions and affect glands. Interneurons connect neurons to other neurons within the same region of the brain or spinal cord.

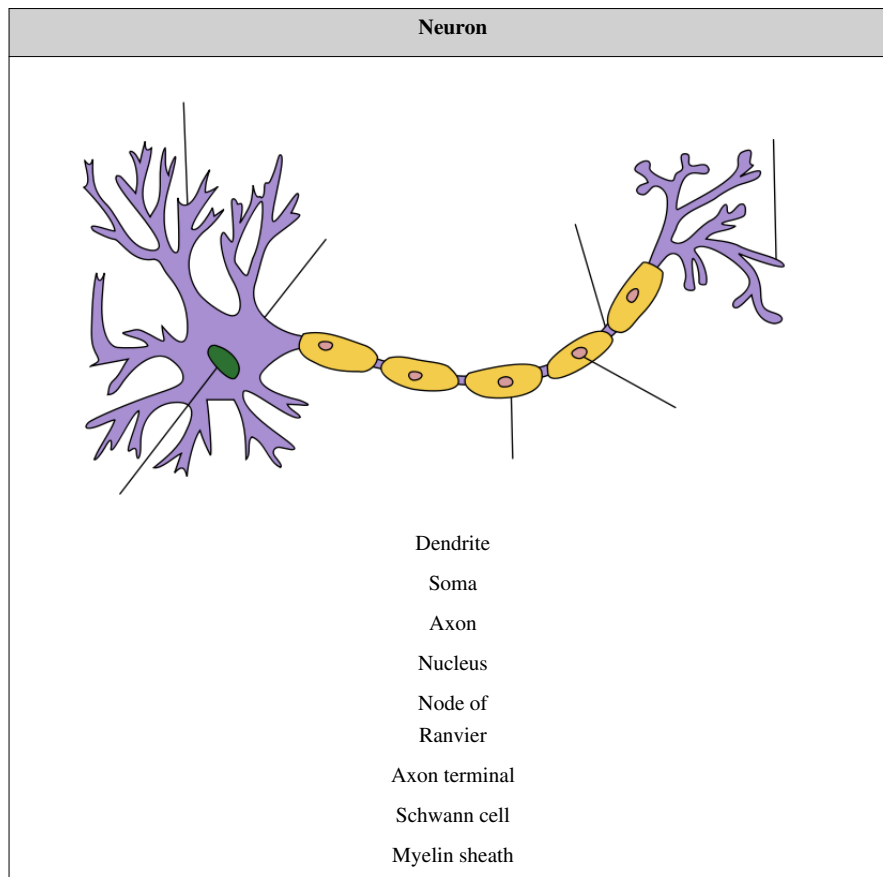
A typical neuron possesses a cell body (often called soma), dendrites, and an axon. Dendrites are filaments of protoplasm that extrude from the cell body, often extending for hundreds of microns and branching multiple times, giving rise to a complex "dendritic tree". An axon is a special protoplasmic filament that arises from the cell body at a site called the axon hillock and travels through the body, often for a great distance. The cell body of a neuron frequently gives rise to multiple dendrites, but never to more than one axon, although the axon may branch hundreds of times before it terminates. At the majority of synapses, signals are sent from the axon of one neuron to a dendrite of another. There are, however, many exceptions to these rules: neurons that lack dendrites, neurons that have no axon, synapses that connect an axon to another axon or a dendrite to another dendrite, etc.

All neurons are electrically excitable, maintaining voltage gradients across their membranes by means of metabolically driven ion pumps, which combine with ion channels embedded in the membrane to generate intracellular-versus-extracellular concentration differences of ions such as sodium, potassium, chloride, and calcium. Changes in the cross-membrane voltage can alter the function of voltage-dependent ion channels. If the voltage changes by a large enough amount, an all-or-none electrochemical pulse called an action potential is generated, which travels rapidly along the cell's axon, and activates synaptic connections with other cells when it arrives.

Neurons do not undergo cell division, and usually cannot be replaced after being lost. In most cases they are generated by special types of stem cells, although astrocytes (a type of glial cell) have been observed to turn into neurons as they are sometimes pluripotent.

## Overview

### Structure of a typical neuron



A neuron is a special type of cell that is found in the bodies of most animals (all members of the group Eumetazoa, to be precise—this excludes only sponges and a few other very simple animals). The features that define a neuron are electrical excitability and the presence of synapses, which are complex membrane junctions used to transmit signals to other cells. The body's neurons, plus the glial cells that give them structural and metabolic support, together constitute the nervous system. In vertebrates, the majority of neurons belong to the central nervous system, but some reside in peripheral ganglia, and many sensory neurons are situated in sensory organs such as the retina and cochlea.

Although neurons are very diverse and there are exceptions to nearly every rule, it is convenient to begin with a schematic description of the structure and function of a "typical" neuron. A typical neuron is divided into three parts: the soma or cell body, dendrites, and axon. The soma is usually compact; the axon and dendrites are filaments that extrude from it. Dendrites typically branch profusely, getting thinner with each branching, and extending their farthest branches a few hundred microns from the soma. The axon leaves the soma at a swelling called the axon hillock, and can extend for great distances, giving rise to hundreds of branches. Unlike dendrites, an axon usually maintains the same diameter as it extends. The soma may give rise to numerous dendrites, but never to more than one axon. Synaptic signals from other neurons are received by the soma and dendrites; signals to other neurons are transmitted by the axon. A typical synapse, then, is a contact between the axon of one neuron and a dendrite or soma of another. Synaptic signals may be excitatory or inhibitory. If the net excitation received by a neuron over a short period of time is large enough, the neuron generates a brief pulse called an action potential, which originates at the soma and propagates rapidly along the axon, activating synapses onto other neurons as it goes.

Many neurons fit the foregoing schema in every respect, but there are also exceptions to most parts of it. There are no neurons that lack a soma, but there are neurons that lack dendrites, and others that lack an axon. Furthermore, in addition to the typical axodendritic and axosomatic synapses, there are axoaxonic (axon-to-axon) and dendrodendritic (dendrite-to-dendrite) synapses.

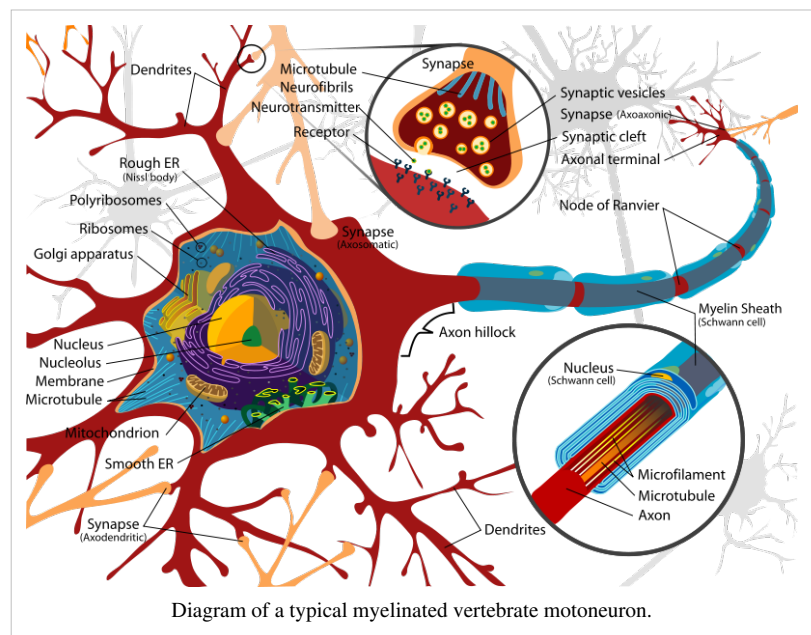
The key to neural function is the synaptic signalling process, which is partly electrical and partly chemical. The electrical aspect depends on properties of the neuron's membrane. Like all animal cells, every neuron is surrounded by a plasma membrane, a bilayer of lipid molecules with many types of protein structures embedded in it. A lipid bilayer is a powerful electrical insulator, but in neurons, many of the protein structures embedded in the membrane are electrically active. These include ion channels that permit electrically charged ions to flow across the membrane, and ion pumps that actively transport ions from one side of the membrane to the other. Most ion channels are permeable only to specific types of ions. Some ion channels are voltage gated, meaning that they can be switched between open and closed states by altering the voltage difference across the membrane. Others are chemically gated, meaning that they can be switched between open and closed states by interactions with chemicals that diffuse through the extracellular fluid. The interactions between ion channels and ion pumps produce a voltage difference across the membrane, typically a bit less than 1/10 of a volt at baseline. This voltage has two functions: first, it provides a power source for an assortment of voltage-dependent protein machinery that is embedded in the membrane; second, it provides a basis for electrical signal transmission between different parts of the membrane.

Neurons communicate by chemical and electrical synapses in a process known as synaptic transmission. The fundamental process that triggers synaptic transmission is the action potential, a propagating electrical signal that is generated by exploiting the electrically excitable membrane of the neuron. This is also known as a wave of depolarization.

## Anatomy and histology

Neurons are highly specialized for the processing and transmission of cellular signals. Given the diversity of functions performed by neurons in different parts of the nervous system, there is, as expected, a wide variety in the shape, size, and electrochemical properties of neurons. For instance, the soma of a neuron can vary from 4 to 100 micrometers in diameter.<sup>[2]</sup>

- The soma is the central part of the neuron. It contains the nucleus of the cell, and therefore is where most protein synthesis occurs. The nucleus ranges from 3 to 18 micrometers in diameter.<sup>[3]</sup>



- The dendrites of a neuron are cellular extensions with many branches, and metaphorically this overall shape and structure is referred to as a dendritic tree. This is where the majority of input to the neuron occurs.
- The axon is a finer, cable-like projection which can extend tens, hundreds, or even tens of thousands of times the diameter of the soma in length. The axon carries nerve signals away from the soma (and also carries some types of information back to it). Many neurons have only one axon, but this axon may—and usually will—undergo extensive branching, enabling communication with many target cells. The part of the axon where it emerges from

the soma is called the axon hillock. Besides being an anatomical structure, the axon hillock is also the part of the neuron that has the greatest density of voltage-dependent sodium channels. This makes it the most easily-excited part of the neuron and the spike initiation zone for the axon: in neurological terms it has the most negative action potential threshold. While the axon and axon hillock are generally involved in information outflow, this region can also receive input from other neurons.

- The axon terminal contains synapses, specialized structures where neurotransmitter chemicals are released in order to communicate with target neurons.

Although the canonical view of the neuron attributes dedicated functions to its various anatomical components, dendrites and axons often act in ways contrary to their so-called main function.

Axons and dendrites in the central nervous system are typically only about one micrometer thick, while some in the peripheral nervous system are much thicker. The soma is usually about 10–25 micrometers in diameter and often is not much larger than the cell nucleus it contains. The longest axon of a human motoneuron can be over a meter long, reaching from the base of the spine to the toes. Sensory neurons have axons that run from the toes to the dorsal columns, over 1.5 meters in adults. Giraffes have single axons several meters in length running along the entire length of their necks. Much of what is known about axonal function comes from studying the squid giant axon, an ideal experimental preparation because of its relatively immense size (0.5–1 millimeters thick, several centimeters long).

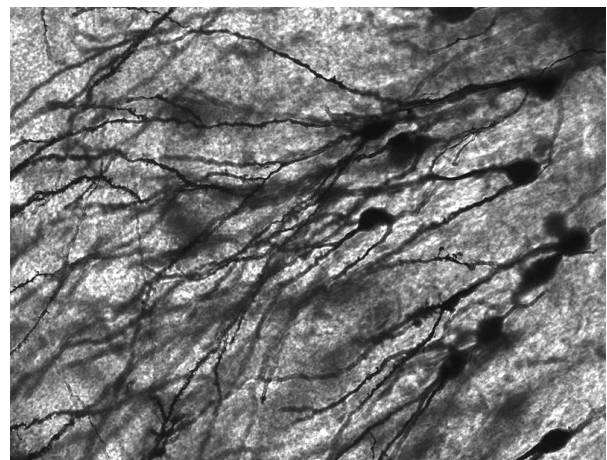
Fully differentiated neurons are permanently amitotic;<sup>[4]</sup> however, recent research shows that additional neurons throughout the brain can originate from neural stem cells found throughout the brain but in particularly high concentrations in the subventricular zone and subgranular zone through the process of neurogenesis.<sup>[5]</sup>

## Histology and internal structure

Nerve cell bodies stained with basophilic dyes show numerous microscopic clumps of **Nissl substance** (named after German psychiatrist and neuropathologist Franz Nissl, 1860–1919), which consists of rough endoplasmic reticulum and associated ribosomal RNA. The prominence of the Nissl substance can be explained by the fact that nerve cells are metabolically very active, and hence are involved in large amounts of protein synthesis.

The cell body of a neuron is supported by a complex meshwork of structural proteins called **neurofilaments**, which are assembled into larger **neurofibrils**. Some neurons also contain pigment granules, such as **neuromelanin** (a brownish-black pigment, byproduct of synthesis of catecholamines) and **lipofuscin** (yellowish-brown pigment that accumulates with age).

There are different internal structural characteristics between axons and dendrites. Typical axons almost never contain ribosomes, except some in the initial segment. Dendrites contain granular endoplasmic reticulum or ribosomes, with diminishing amounts with distance from the cell body.



Golgi-stained neurons in human hippocampal tissue.



## Classes

Neurons exist in a number of different shapes and sizes and can be classified by their morphology and function. The anatomist Camillo Golgi grouped neurons into two types; type I with long axons used to move signals over long distances and type II with short axons, which can often be confused with dendrites. Type I cells can be further divided by where the cell body or soma is located. The basic morphology of type I neurons, represented by spinal motor neurons, consists of a cell body called the soma and a long thin axon which is covered by the myelin sheath. Around the cell body is a branching dendritic tree that receives signals from other neurons. The end of the axon has branching terminals (axon terminal) that release neurotransmitters into a gap called the synaptic cleft between the terminals and the dendrites of the next neuron.

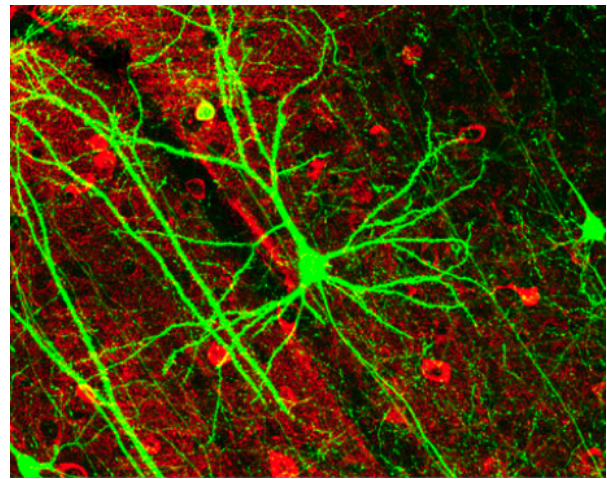


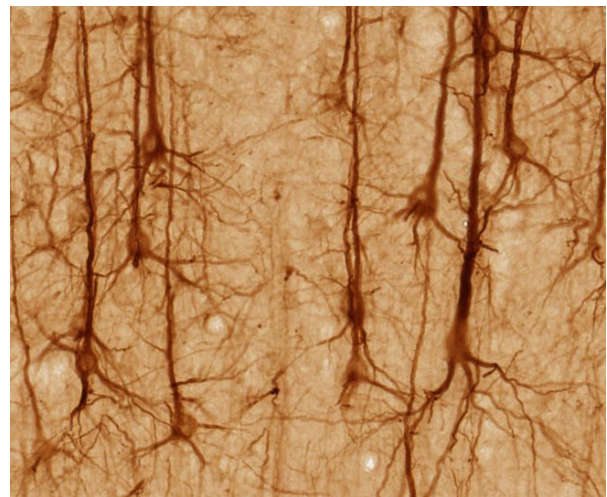
Image of pyramidal neurons in mouse cerebral cortex expressing green fluorescent protein. The red staining indicates GABAergic interneurons. Source PLoS Biology [6]

## Structural classification

### Polarity

Most neurons can be anatomically characterized as:

- Unipolar or pseudounipolar: dendrite and axon emerging from same process.
- Bipolar: axon and single dendrite on opposite ends of the soma.
- Multipolar: more than two dendrites:
  - Golgi I: neurons with long-projecting axonal processes; examples are pyramidal cells, Purkinje cells, and anterior horn cells.
  - Golgi II: neurons whose axonal process projects locally; the best example is the granule cell.



SMI32-stained pyramidal neurons in cerebral cortex.

### Other

Furthermore, some unique neuronal types can be identified according to their location in the nervous system and distinct shape. Some examples are:

- Basket cells, neurons with dilated and knotty dendrites in the cerebellum.
- Betz cells, large motor neurons.
- Medium spiny neurons, most neurons in the corpus striatum.
- Purkinje cells, huge neurons in the cerebellum, a type of Golgi I multipolar neuron.
- Pyramidal cells, neurons with triangular soma, a type of Golgi I.
- Renshaw cells, neurons with both ends linked to alpha motor neurons.
- Granule cells, a type of Golgi II neuron.
- anterior horn cells, motoneurons located in the spinal cord.



## Functional classification

### Direction

- Afferent neurons convey information from tissues and organs into the central nervous system and are sometimes also called sensory neurons.
- Efferent neurons transmit signals from the central nervous system to the effector cells and are sometimes called motor neurons.
- Interneurons connect neurons within specific regions of the central nervous system.

Afferent and efferent can also refer generally to neurons which, respectively, bring information to or send information from the brain region.

### Action on other neurons

A neuron affects other neurons by releasing a neurotransmitter that binds to chemical receptors. The effect upon the target neuron is determined not by the source neuron or by the neurotransmitter, but by the type of receptor that is activated. A neurotransmitter can be thought of as a key, and a receptor as a lock: the same type of key can here be used to open many different types of locks. Receptors can be classified broadly as *excitatory* (causing an increase in firing rate), *inhibitory* (causing a decrease in firing rate), or *modulatory* (causing long-lasting effects not directly related to firing rate).

In fact, however, the two most common neurotransmitters in the brain, glutamate and GABA, have actions that are largely consistent. Glutamate acts on several different types of receptors, but most of them have effects that are excitatory. Similarly GABA acts on several different types of receptors, but all of them have effects (in adult animals, at least) that are inhibitory. Because of this consistency, it is common for neuroscientists to simplify the terminology by referring to cells that release glutamate as "excitatory neurons," and cells that release GABA as "inhibitory neurons." Since well over 90% of the neurons in the brain release either glutamate or GABA, these labels encompass the great majority of neurons. There are also other types of neurons that have consistent effects on their targets, for example "excitatory" motor neurons in the spinal cord that release acetylcholine, and "inhibitory" spinal neurons that release glycine.

The distinction between excitatory and inhibitory neurotransmitters is not absolute, however. Rather, it depends on the class of chemical receptors present on the target neuron. In principle, a single neuron, releasing a single neurotransmitter, can have excitatory effects on some targets, inhibitory effects on others, and modulatory effects on other still. For example, photoreceptors in the retina constantly release the neurotransmitter glutamate in the absence of light. So-called OFF bipolar cells are, like most neurons, excited by the released glutamate. However, neighboring target neurons called ON bipolar cells are instead *inhibited* by glutamate, because they lack the typical ionotropic glutamate receptors and instead express a class of inhibitory metabotropic glutamate receptors.<sup>[7]</sup> When light is present, the photoreceptors cease releasing glutamate, which relieves the ON bipolar cells from inhibition, activating them; this simultaneously removes the excitation from the OFF bipolar cells, silencing them.

### Discharge patterns

Neurons can be classified according to their electrophysiological characteristics:

- **Tonic or regular spiking.** Some neurons are typically constantly (or tonically) active. Example: interneurons in neurostriatum.
  - **Phasic or bursting.** Neurons that fire in bursts are called phasic.
  - **Fast spiking.** Some neurons are notable for their fast firing rates, for example some types of cortical inhibitory interneurons, cells in globus pallidus, retinal ganglion cells.<sup>[8] [9]</sup>
  - **Thin-spike.** Action potentials of some neurons are more narrow compared to the others. For example, interneurons in the prefrontal cortex are thin-spike neurons.
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### Classification by neurotransmitter production

Neurons differ in the type of neurotransmitter they manufacture. Some examples are

- cholinergic neurons - acetylcholine

Acetylcholine is released from presynaptic neurons into the synaptic cleft. It acts as a ligand for Nicotinic Acetylcholine receptors, which are ligand gated  $\text{Na}^+$  ion channels. Ligand binding opens the channel causing depolarization and increases the probability of an action potential firing, occurring once the threshold is reached.

- GABAergic neurons - gamma aminobutyric acid

GABA is one of two neuroinhibitors in the CNS, the other being Glycine. GABA has a homologous function to ACh, gating anion channels that allow  $\text{Cl}^-$  ions to enter the post synaptic neuron.  $\text{Cl}^-$  causes hyperpolarization within the neuron, decreasing the probability of an action potential firing as the voltage becomes more negative (recall that for an action potential to fire, a positive voltage threshold must be reached).

- glutamatergic neurons - glutamate

Glutamate is one of two primary neuroexcitators, the other being Aspartate (not Aspartame). Glutamate receptors are one of four categories, three of which are ion channels and one of which is a G-protein coupled receptor (often referred to as GPCR). 1 - AMPA and Kainate receptors (really two different receptors) both function as  $\text{Na}^+$  cation channels mediating fast excitatory synaptic transmission 2 - NMDA receptors are another cation channel, instead for  $\text{Ca}^{++}$ . The function of NMDA receptors is dependant on Glycine binding to a mediator binding spot on the channel pore. NMDA receptors will not function without both ligands present - antagonist drugs for Glycine will cause NMDA receptors to malfunction. 3 - Metabotropic receptor, a GPCR that modulates synaptic transmission Glutamate can cause excitotoxicity when blood flow to the brain is interrupted, resulting in brain damage. When blood flow is suppressed, glutamate is released from presynaptic neurons causing NMDA and AMPA receptor activation more so than would normally be the case outside of stress conditions, leading to elevated  $\text{Ca}^{++}$  and  $\text{Na}^+$  entering the post synaptic neuron and cell damage.

- dopaminergic neurons - dopamine

Dopamine is a neurotransmitter that acts on a GPCR. Dopamine is connected to mood and behaviour, and modulates post synaptic neurotransmission. Loss of dopamine neurons has been linked to Parkinson's disease, schizophrenia, and ADD.

- serotonergic neurons - serotonin

Serotonin, full name 5-Hydroxytryptamine, can act as excitatory or inhibitory. Of the four 5HT receptor classes, 3 are GPCR and 1 is ligand gated cation channel. Serotonin is synthesized from tryptophan by tryptophan hydroxylase, and then further by aromatic acid decarboxylase. A lack of 5HT at postsynaptic neurons has been linked to depression. Drugs that are antagonistic for reabsorption by presynaptic neurons are used for treatment, such as Prozac and Zoloft.

### Connectivity

Neurons communicate with one another via synapses, where the axon terminal or *en passant* boutons (terminals located along the length of the axon) of one cell impinges upon another neuron's dendrite, soma or, less commonly, axon. Neurons such as Purkinje cells in the cerebellum can have over 1000 dendritic branches, making connections with tens of thousands of other cells; other neurons, such as the magnocellular neurons of the supraoptic nucleus, have only one or two dendrites, each of which receives thousands of synapses. Synapses can be excitatory or inhibitory and will either increase or decrease activity in the target neuron. Some neurons also communicate via electrical synapses, which are direct, electrically-conductive junctions between cells.

In a chemical synapse, the process of synaptic transmission is as follows: when an action potential reaches the axon terminal, it opens voltage-gated calcium channels, allowing calcium ions to enter the terminal. Calcium causes

synaptic vesicles filled with neurotransmitter molecules to fuse with the membrane, releasing their contents into the synaptic cleft. The neurotransmitters diffuse across the synaptic cleft and activate receptors on the postsynaptic neuron.

The human brain has a huge number of synapses. Each of the  $10^{11}$  (one hundred billion) neurons has on average 7,000 synaptic connections to other neurons. It has been estimated that the brain of a three-year-old child has about  $10^{15}$  synapses (1 quadrillion). This number declines with age, stabilizing by adulthood. Estimates vary for an adult, ranging from  $10^{14}$  to  $5 \times 10^{14}$  synapses (100 to 500 trillion).<sup>[10]</sup>

## Mechanisms for propagating action potentials

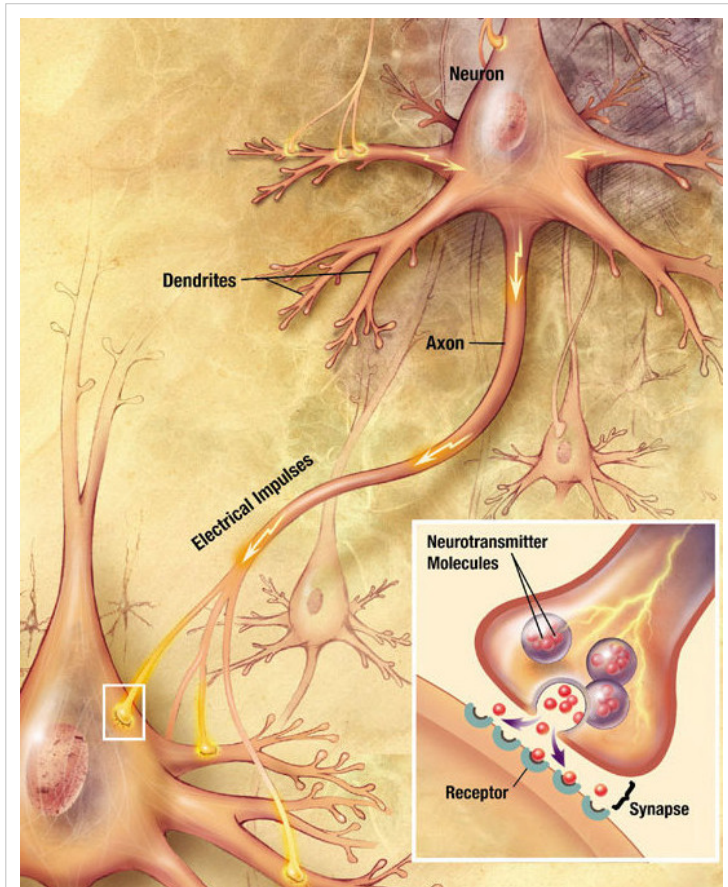
In 1937, John Zachary Young suggested that the squid giant axon could be used to study neuronal electrical properties.<sup>[11]</sup> Being larger than but similar in nature to human neurons, squid cells were easier to study. By inserting electrodes into the giant squid axons, accurate measurements were made of the membrane potential.

The cell membrane of the axon and soma contain voltage-gated ion channels which allow the neuron to generate and propagate an electrical signal (an action potential). These signals are generated and propagated by charge-carrying ions including sodium ( $\text{Na}^+$ ), potassium ( $\text{K}^+$ ), chloride ( $\text{Cl}^-$ ), and calcium ( $\text{Ca}^{2+}$ ).

There are several stimuli that can activate a neuron leading to electrical activity, including pressure, stretch, chemical transmitters, and changes of the electric potential across the cell membrane.<sup>[12]</sup> Stimuli cause specific ion-channels within the cell membrane to open, leading to a flow of ions through the cell membrane, changing the membrane potential.

Thin neurons and axons require less metabolic expense to produce and carry action potentials, but thicker axons convey impulses more rapidly. To minimize metabolic expense while maintaining rapid conduction, many neurons have insulating sheaths of myelin around their axons. The sheaths are formed by glial cells: oligodendrocytes in the central nervous system and Schwann cells in the peripheral nervous system. The sheath enables action potentials to travel faster than in unmyelinated axons of the same diameter, whilst using less energy. The myelin sheath in peripheral nerves normally runs along the axon in sections about 1 mm long, punctuated by unsheathed nodes of Ranvier which contain a high density of voltage-gated ion channels. Multiple sclerosis is a neurological disorder that results from demyelination of axons in the central nervous system.

Some neurons do not generate action potentials, but instead generate a graded electrical signal, which in turn causes graded neurotransmitter release. Such nonspiking neurons tend to be sensory neurons or interneurons, because they cannot carry signals long distances.



A signal propagating down an axon to the cell body and dendrites of the next cell.

## All-or-none principle

The conduction of nerve impulses is an example of an all-or-none response. In other words, if a neuron responds at all, then it must respond completely. The greater the intensity of stimulation does not produce a stronger signal but can produce *more* impulses per second. There are different types of receptor response to stimulus, slowly adapting or tonic receptors respond to steady stimulus and produce a steady rate of firing. These tonic receptors most often respond to increased intensity of stimulus by increasing their firing frequency, usually as a power function of stimulus plotted against impulses per second. This can be likened to an intrinsic property of light where to get greater intensity of a specific frequency (color) there has to be more photons, as the photons can't become "stronger" for a specific frequency.

There are a number of other receptor types that are called quickly adapting or phasic receptors, where firing decreases or stops with steady stimulus; examples include: skin when touched by an object causes the neurons to fire, but if the object maintains even pressure against the skin the neurons stop firing. The neurons of the skin and muscles that are responsive to pressure and vibration have filtering accessory structures that aid their function. The pacinian corpuscle is one such structure; it has concentric layers like an onion which form around the axon terminal. When pressure is applied and the corpuscle is deformed, mechanical stimulus is transferred to the axon, which fires. If the pressure is steady there is no more stimulus, thus typically these neurons respond with a transient depolarization during the initial deformation and again when the pressure is removed which cause the corpuscle to change shape again. Other types of adaptation are important in extending the function of a number of other neurons.<sup>[13]</sup>

## History

The term *neuron* was coined by the German anatomist Heinrich Wilhelm Waldeyer. The neuron's place as the primary functional unit of the nervous system was first recognized in the early 20th century through the work of the Spanish anatomist Santiago Ramón y Cajal.<sup>[14]</sup> Cajal proposed that neurons were discrete cells that communicated with each other via specialized junctions, or spaces, between cells.<sup>[14]</sup> This became known as the neuron doctrine, one of the central tenets of modern neuroscience.<sup>[14]</sup> To observe the structure of individual neurons, Cajal used a silver staining method developed by his rival, Camillo Golgi.<sup>[14]</sup> The Golgi stain is an extremely useful method for neuroanatomical investigations because, for reasons unknown, it stains a very small percentage of cells in a tissue, so one is able to see the complete micro structure of individual neurons without much overlap from other cells in the densely packed brain.<sup>[15]</sup>

## The neuron doctrine

The **neuron doctrine** is the now fundamental idea that neurons are the basic structural and functional units of the nervous system. The theory was put forward by Santiago Ramón y Cajal in the late 19th century. It held that neurons are discrete cells (not connected in a meshwork), acting as metabolically distinct units.

Later discoveries yielded a few refinements to the simplest form of the doctrine. For example, glial cells, which are not considered neurons, play an essential role in information processing.<sup>[16]</sup> Also, electrical synapses are more common than previously thought,<sup>[17]</sup> meaning that there are direct, cytoplasmic connections between neurons. In fact, there are examples of neurons forming even tighter coupling; the squid giant axon arises from the fusion of multiple neurons that retain individual cell bodies and the crayfish giant axon consists of a series of neurons with high conductance septate junctions.

Cajal also postulated the **Law of Dynamic Polarization**, which states that a neuron receives signals at its dendrites and cell body and transmits them, as action potentials, along the axon in one direction: away from the cell body.<sup>[18]</sup> The Law of Dynamic Polarization has important exceptions; dendrites can serve as synaptic output sites of neurons<sup>[19]</sup> and axons can receive synaptic inputs.

## Neurons in the brain

The number of neurons in the brain varies dramatically from species to species.<sup>[20]</sup> One estimate puts the human brain at about 100 billion (  $10^{11}$  ) neurons and 100 trillion (  $10^{14}$  ) synapses.<sup>[20]</sup> Another estimate is 86 billion neurons of which 16.3 are in the cerebral cortex and 69 in the cerebellum.<sup>[21]</sup> By contrast, the nematode worm *Caenorhabditis elegans* has just 302 neurons making it an ideal experimental subject as scientists have been able to map all of the organism's neurons. The fruit fly *Drosophila melanogaster*, a common subject in biology experiments, has around 100,000 neurons and exhibits many complex behaviors. Many properties of neurons, from the type of neurotransmitters used to ion channel composition, are maintained across species, allowing scientists to study processes occurring in more complex organisms in much simpler experimental systems.

## Neurological disorders

**Charcot-Marie-Tooth disease** (CMT), also known as Hereditary Motor and Sensory Neuropathy (HMSN), Hereditary Sensorimotor Neuropathy (HMSN), or Peroneal Muscular Atrophy, is a heterogeneous inherited disorder of nerves (neuropathy) that is characterized by loss of muscle tissue and touch sensation, predominantly in the feet and legs but also in the hands and arms in the advanced stages of disease. Presently incurable, this disease is one of the most common inherited neurological disorders, with 37 in 100,000 affected.

**Alzheimer's disease** (AD), also known simply as Alzheimer's, is a neurodegenerative disease characterized by progressive cognitive deterioration together with declining activities of daily living and neuropsychiatric symptoms or behavioral changes. The most striking early symptom is loss of short-term memory (amnesia), which usually manifests as minor forgetfulness that becomes steadily more pronounced with illness progression, with relative preservation of older memories. As the disorder progresses, cognitive (intellectual) impairment extends to the domains of language (aphasia), skilled movements (apraxia), recognition (agnosia), and functions such as decision-making and planning get impaired.

**Parkinson's disease** (also known as Parkinson disease or PD) is a degenerative disorder of the central nervous system that often impairs the sufferer's motor skills and speech. Parkinson's disease belongs to a group of conditions called movement disorders. It is characterized by muscle rigidity, tremor, a slowing of physical movement (bradykinesia), and in extreme cases, a loss of physical movement (akinesia). The primary symptoms are the results of decreased stimulation of the motor cortex by the basal ganglia, normally caused by the insufficient formation and action of dopamine, which is produced in the dopaminergic neurons of the brain. Secondary symptoms may include high level cognitive dysfunction and subtle language problems. PD is both chronic and progressive.

**Myasthenia Gravis** is a neuromuscular disease leading to fluctuating muscle weakness and fatigability. Weakness is typically caused by circulating antibodies that block acetylcholine receptors at the post-synaptic neuromuscular junction, inhibiting the stimulative effect of the neurotransmitter acetylcholine. Myasthenia is treated with immunosuppressants, cholinesterase inhibitors and, in selected cases, thymectomy.

## Demyelination

Demyelination is the act of demyelinating, or the loss of the myelin sheath insulating the nerves. When myelin degrades, conduction of signals along the nerve can be impaired or lost, and the nerve eventually withers. This leads to certain neurodegenerative disorders like multiple sclerosis, chronic inflammatory demyelinating polyneuropathy.

## Axonal degeneration

Although most injury responses include a calcium influx signaling to promote resealing of severed parts, axonal injuries initially lead to acute axonal degeneration (AAD), which is rapid separation of the proximal and distal ends within 30 minutes of injury. Degeneration follows with swelling of the axolemma, and eventually leads to bead like formation. Granular disintegration of the axonal cytoskeleton and inner organelles occurs after axolemma

degradation. Early changes include accumulation of mitochondria in the paranodal regions at the site of injury. Endoplasmic reticulum degrades and mitochondria swell up and eventually disintegrate. The disintegration is dependent on Ubiquitin and Calpain proteases (caused by influx of calcium ion), suggesting that axonal degeneration is an active process. Thus the axon undergoes complete fragmentation. The process takes about roughly 24 hrs in the PNS, and longer in the CNS. The signaling pathways leading to axolemma degeneration are currently unknown.

## Nerve regeneration

Although neurons do not divide or replicate in most parts of the adult vertebrate brain, it is often possible for axons to regrow if they are severed. This can take a long time: after a nerve injury to the human arm, for example, it may take months for feeling to return to the hands and fingers.

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## External links

- NeuronBank<sup>[22]</sup> an online neuromics tool for cataloging neuronal types and synaptic connectivity.
- High Resolution Neuroanatomical Images of Primate and Non-Primate Brains<sup>[23]</sup>.
- The Department of Neuroscience at Wikiversity, which presently offers two courses: Fundamentals of Neuroscience and Comparative Neuroscience.
- NIF Search - Renshaw Cell<sup>[24]</sup> via the Neuroscience Information Framework
- Cell Centered Database - Neuron<sup>[25]</sup>
- NeuroMorpho.Org<sup>[26]</sup> an online database of digital reconstructions of neuronal morphology.
- Immunohistochemistry Image Gallery: Neuron<sup>[27]</sup>

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# Neurophysiology

**Neurophysiology** (from Greek νεῦρον, *neuron*, "nerve"; φύσις, *physis*, "nature, origin"; and -λογία, *-logia*) is a part of physiology. Neurophysiology is the study of nervous system function. Primarily, it is connected with neurobiology, psychology, neurology, clinical neurophysiology, electrophysiology, biophysical neurophysiology, ethology, neuroanatomy, cognitive science and other brain sciences.<sup>[1]</sup>

## See also

- electrophysiology
- neuroscience
- brain
- neural coding
- neurology

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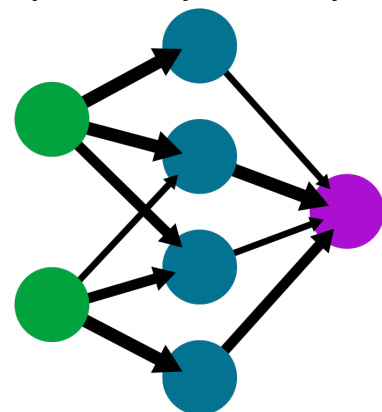
# Neural network

Traditionally, the term **neural network** had been used to refer to a network or circuit of biological neurons. The modern usage of the term often refers to artificial neural networks, which are composed of artificial neurons or nodes. Thus the term has two distinct usages:

1. Biological neural networks are made up of real biological neurons that are connected or functionally related in the peripheral nervous system or the central nervous system. In the field of neuroscience, they are often identified as groups of neurons that perform a specific physiological function in laboratory analysis.
2. Artificial neural networks are made up of interconnecting artificial neurons (programming constructs that mimic the properties of biological neurons). Artificial neural networks may either be used to gain an understanding of biological neural networks, or for solving artificial intelligence problems without necessarily creating a model of a real biological system. The real, biological nervous system is highly complex and includes some features that may seem superfluous based on an understanding of artificial networks.

### A simple neural network

input layer      hidden layer      output layer



Simplified view of a feedforward artificial neural network

This article focuses on the relationship between the two concepts; for detailed coverage of the two different concepts refer to the separate articles: Biological neural network and Artificial neural network.



## Overview

In general a biological neural network is composed of a group or groups of chemically connected or functionally associated neurons. A single neuron may be connected to many other neurons and the total number of neurons and connections in a network may be extensive. Connections, called synapses, are usually formed from axons to dendrites, though dendrodendritic microcircuits<sup>[1]</sup> and other connections are possible. Apart from the electrical signaling, there are other forms of signaling that arise from neurotransmitter diffusion, which have an effect on electrical signaling. As such, neural networks are extremely complex.

Artificial intelligence and cognitive modeling try to simulate some properties of neural networks. While similar in their techniques, the former has the aim of solving particular tasks, while the latter aims to build mathematical models of biological neural systems.

In the artificial intelligence field, artificial neural networks have been applied successfully to speech recognition, image analysis and adaptive control, in order to construct software agents (in computer and video games) or autonomous robots. Most of the currently employed artificial neural networks for artificial intelligence are based on statistical estimation, optimization and control theory.

The cognitive modelling field involves the physical or mathematical modeling of the behaviour of neural systems; ranging from the individual neural level (e.g. modelling the spike response curves of neurons to a stimulus), through the neural cluster level (e.g. modelling the release and effects of dopamine in the basal ganglia) to the complete organism (e.g. behavioural modelling of the organism's response to stimuli). Artificial intelligence, cognitive modelling, and neural networks are information processing paradigms inspired by the way biological neural systems process data.

## History of the neural network analogy

The concept neural networks started in the late-1800s as an effort to describe how the human mind performed. These ideas started being applied to computational models with Turing's B-type machines and the perceptron.

In early 1950s Friedrich Hayek was one of the first to posit the idea of spontaneous order in the brain arising out of decentralized networks of simple units (neurons). In the late 1940s, Donald Hebb made one of the first hypotheses for a mechanism of neural plasticity (i.e. learning), Hebbian learning. Hebbian learning is considered to be a 'typical' unsupervised learning rule and it (and variants of it) was an early model for long term potentiation.

The perceptron is essentially a linear classifier for classifying data  $x \in R^n$  specified by parameters  $w \in R^n, b \in R$  and an output function  $f = w'x + b$ . Its parameters are adapted with an ad-hoc rule similar to stochastic steepest gradient descent. Because the inner product is a linear operator in the input space, the Perceptron can only perfectly classify a set of data for which different classes are linearly separable in the input space, while it often fails completely for non-separable data. While the development of the algorithm initially generated some enthusiasm, partly because of its apparent relation to biological mechanisms, the later discovery of this inadequacy caused such models to be abandoned until the introduction of non-linear models into the field.

The cognitron (1975) was an early multilayered neural network with a training algorithm. The actual structure of the network and the methods used to set the interconnection weights change from one neural strategy to another, each with its advantages and disadvantages. Networks can propagate information in one direction only, or they can bounce back and forth until self-activation at a node occurs and the network settles on a final state. The ability for bi-directional flow of inputs between neurons/nodes was produced with the Hopfield's network (1982), and specialization of these node layers for specific purposes was introduced through the first hybrid network.

The parallel distributed processing of the mid-1980s became popular under the name connectionism.

The rediscovery of the backpropagation algorithm was probably the main reason behind the repopularisation of neural networks after the publication of "Learning Internal Representations by Error Propagation" in 1986 (Though backpropagation itself dates from 1974). The original network utilised multiple layers of weight-sum units of the

type  $f = g(w'x + b)$ , where  $g$  was a sigmoid function or logistic function such as used in logistic regression. Training was done in the form of stochastic steepest gradient descent. The employment of the chain rule of differentiation in deriving the appropriate parameter updates results in an algorithm that seems to 'backpropagate errors', hence the nomenclature. However it is essentially a form of gradient descent. Determining the optimal parameters in a model of this type is not trivial, and steepest gradient descent methods cannot be relied upon to give the solution without a good starting point. In recent times, networks with the same architecture as the backpropagation network are referred to as Multi-Layer Perceptrons. This name does not impose any limitations on the type of algorithm used for learning. The backpropagation network generated much enthusiasm at the time and there was much controversy about whether such learning could be implemented in the brain or not, partly because a mechanism for reverse signalling was not obvious at the time, but most importantly because there was no plausible source for the 'teaching' or 'target' signal.

## The brain, neural networks and computers

Neural networks, as used in artificial intelligence, have traditionally been viewed as simplified models of neural processing in the brain, even though the relation between this model and brain biological architecture is debated.

A subject of current research in theoretical neuroscience is the question surrounding the degree of complexity and the properties that individual neural elements should have to reproduce something resembling animal intelligence.

Historically, computers evolved from the von Neumann architecture, which is based on sequential processing and execution of explicit instructions. On the other hand, the origins of neural networks are based on efforts to model information processing in biological systems, which may rely largely on parallel processing as well as implicit instructions based on recognition of patterns of 'sensory' input from external sources. In other words, at its very heart a neural network is a complex statistical processor (as opposed to being tasked to sequentially process and execute).

## Neural networks and artificial intelligence

A *neural network* (NN), in the case of artificial neurons called *artificial neural network* (ANN) or *simulated neural network* (SNN), is an interconnected group of natural or artificial neurons that uses a mathematical or computational model for information processing based on a connectionistic approach to computation. In most cases an ANN is an adaptive system that changes its structure based on external or internal information that flows through the network.

In more practical terms neural networks are non-linear statistical data modeling or decision making tools. They can be used to model complex relationships between inputs and outputs or to find patterns in data.

However, the paradigm of neural networks - i.e., *implicit*, and not *explicit* learning is stressed - seems more to correspond to some kind of *natural intelligence* than to the traditional *Artificial Intelligence*, which would stress, instead, rule-based learning as at school.

## Background

An artificial neural network involves a network of simple processing elements (artificial neurons) which can exhibit complex global behavior, determined by the connections between the processing elements and element parameters. Artificial neurons were first proposed in 1943 by Warren McCulloch, a neurophysiologist, and Walter Pitts, an MIT logician.[2] One classical type of artificial neural network is the recurrent Hopfield net.

In a neural network model simple nodes, which can be called variously "neurons", "neurodes", "Processing Elements" (PE) or "units", are connected together to form a network of nodes — hence the term "neural network". While a neural network does not have to be adaptive *per se*, its practical use comes with algorithms designed to alter the strength (weights) of the connections in the network to produce a desired signal flow.

In modern software implementations of artificial neural networks the approach inspired by biology has more or less been abandoned for a more practical approach based on statistics and signal processing. In some of these systems, neural networks, or parts of neural networks (such as artificial neurons), are used as components in larger systems

that combine both adaptive and non-adaptive elements.

The concept of a neural network appears to have first been proposed by Alan Turing in his 1948 paper "Intelligent Machinery".

## Applications of natural and of artificial neural networks

The utility of artificial neural network models lies in the fact that they can be used to infer a function from observations and also to use it. This is particularly useful in applications where the complexity of the data or task makes the design of such a function by hand impractical.

### Real life applications

The tasks to which artificial neural networks are applied tend to fall within the following broad categories:

- Function approximation, or regression analysis, including time series prediction and modelling.
- Classification, including pattern and sequence recognition, novelty detection and sequential decision making.
- Data processing, including filtering, clustering, blind signal separation and compression.

Application areas of ANNs include system identification and control (vehicle control, process control), game-playing and decision making (backgammon, chess, racing), pattern recognition (radar systems, face identification, object recognition, etc.), sequence recognition (gesture, speech, handwritten text recognition), medical diagnosis, financial applications, data mining (or knowledge discovery in databases, "KDD"), visualization and e-mail spam filtering.

- Moreover, some brain diseases, e.g. Alzheimer, are apparently, and essentially, diseases of the brain's natural NN by damaging necessary prerequisites for the functioning of the mutual interconnections between neurons and/or the so-called glia.

### Use in Teaching Strategy

Neural Networks are being used to determine the significance of a seating arrangement in a classroom learning environment. In this application, neural networks have proven that there is a correlation between the location of high and low-performing students in the room and how well they do in the class. An article in *Complexity* explains that when low-performing students are seated in the front, their chance to do better increases. The results of high-performing students who are seated in the back are not affected. In addition, when high-performing students are seated in the outer four corners, the performance of the class as a whole increases.<sup>[3]</sup> [4]

## Neural network software

*Main article:* Neural network software

**Neural network software** is used to simulate, research, develop and apply artificial neural networks, biological neural networks and in some cases a wider array of adaptive systems.

## Learning paradigms

There are three major learning paradigms, each corresponding to a particular abstract learning task. These are supervised learning, unsupervised learning and reinforcement learning. Usually any given type of network architecture can be employed in any of those tasks.

### Supervised learning

In supervised learning, we are given a set of example pairs  $(x, y)$ ,  $x \in X$ ,  $y \in Y$  and the aim is to find a function  $f$  in the allowed class of functions that matches the examples. In other words, we wish to *infer* how the mapping implied by the data and the cost function is related to the mismatch between our mapping and the data.

### Unsupervised learning

In unsupervised learning we are given some data  $x$ , and a cost function which is to be minimized which can be any function of  $x$  and the network's output,  $f$ . The cost function is determined by the task formulation. Most

applications fall within the domain of estimation problems such as statistical modeling, compression, filtering, blind source separation and clustering.

### Reinforcement learning

In reinforcement learning, data  $x$  is usually not given, but generated by an agent's interactions with the environment. At each point in time  $t$ , the agent performs an action  $y_t$  and the environment generates an observation  $x_t$  and an instantaneous cost  $c_t$ , according to some (usually unknown) dynamics. The aim is to discover a *policy* for selecting actions that minimizes some measure of a long-term cost, i.e. the expected cumulative cost. The environment's dynamics and the long-term cost for each policy are usually unknown, but can be estimated. ANNs are frequently used in reinforcement learning as part of the overall algorithm. Tasks that fall within the paradigm of reinforcement learning are control problems, games and other sequential decision making tasks.

### Learning algorithms

There are many algorithms for training neural networks; most of them can be viewed as a straightforward application of optimization theory and statistical estimation. They include: Back propagation by gradient descent, Rprop, BFGS, CG etc.

Evolutionary computation methods, simulated annealing, expectation maximization and non-parametric methods are among other commonly used methods for training neural networks. See also machine learning.

Recent developments in this field also saw the use of particle swarm optimization and other swarm intelligence techniques used in the training of neural networks.

## Neural networks and neuroscience

Theoretical and computational neuroscience is the field concerned with the theoretical analysis and computational modeling of biological neural systems. Since neural systems are intimately related to cognitive processes and behaviour, the field is closely related to cognitive and behavioural modeling.

The aim of the field is to create models of biological neural systems in order to understand how biological systems work. To gain this understanding, neuroscientists strive to make a link between observed biological processes (data), biologically plausible mechanisms for neural processing and learning (biological neural network models) and theory (statistical learning theory and information theory).

### Types of models

Many models are used in the field, each defined at a different level of abstraction and trying to model different aspects of neural systems. They range from models of the short-term behaviour of individual neurons, through models of how the dynamics of neural circuitry arise from interactions between individual neurons, to models of how behaviour can arise from abstract neural modules that represent complete subsystems. These include models of the long-term and short-term plasticity of neural systems and its relation to learning and memory, from the individual neuron to the system level.

## Current research

While initially research had been concerned mostly with the electrical characteristics of neurons, a particularly important part of the investigation in recent years has been the exploration of the role of neuromodulators such as dopamine, acetylcholine, and serotonin on behaviour and learning.

Biophysical models, such as BCM theory, have been important in understanding mechanisms for synaptic plasticity, and have had applications in both computer science and neuroscience. Research is ongoing in understanding the computational algorithms used in the brain, with some recent biological evidence for radial basis networks and neural backpropagation as mechanisms for processing data.

## Criticism

A common criticism of neural networks, particularly in robotics, is that they require a large diversity of training for real-world operation. Dean Pomerleau, in his research presented in the paper "Knowledge-based Training of Artificial Neural Networks for Autonomous Robot Driving," uses a neural network to train a robotic vehicle to drive on multiple types of roads (single lane, multi-lane, dirt, etc.). A large amount of his research is devoted to (1) extrapolating multiple training scenarios from a single training experience, and (2) preserving past training diversity so that the system does not become overtrained (if, for example, it is presented with a series of right turns – it should not learn to always turn right). These issues are common in neural networks that must decide from amongst a wide variety of responses.

A. K. Dewdney, a former *Scientific American* columnist, wrote in 1997, "Although neural nets do solve a few toy problems, their powers of computation are so limited that I am surprised anyone takes them seriously as a general problem-solving tool." (Dewdney, p. 82)

Arguments for Dewdney's position are that to implement large and effective software neural networks, much processing and storage resources need to be committed. While the brain has hardware tailored to the task of processing signals through a graph of neurons, simulating even a most simplified form on Von Neumann technology may compel a NN designer to fill many millions of database rows for its connections - which can lead to abusive RAM and HD necessities. Furthermore, the designer of NN systems will often need to simulate the transmission of signals through many of these connections and their associated neurons - which must often be matched with incredible amounts of CPU processing power and time. While neural networks often yield *effective* programs, they too often do so at the cost of time and money *efficiency*.

Arguments against Dewdney's position are that neural nets have been successfully used to solve many complex and diverse tasks, ranging from autonomously flying aircraft[5] to detecting credit card fraud[6].

Technology writer Roger Bridgman commented on Dewdney's statements about neural nets:

Neural networks, for instance, are in the dock not only because they have been hyped to high heaven, (what hasn't?) but also because you could create a successful net without understanding how it worked: the bunch of numbers that captures its behaviour would in all probability be "an opaque, unreadable table...valueless as a scientific resource".

In spite of his emphatic declaration that science is not technology, Dewdney seems here to pillory neural nets as bad science when most of those devising them are just trying to be good engineers. An unreadable table that a useful machine could read would still be well worth having.<sup>[7]</sup>

Some other criticisms came from believers of hybrid models (combining neural networks and symbolic approaches). They advocate the intermix of these two approaches and believe that hybrid models can better capture the mechanisms of the human mind (Sun and Bookman 1994).

## See also

- ADALINE
- Artificial neural network
- Biological cybernetics
- Biologically inspired computing
- Cerebellar Model Articulation Controller
- Cognitive architecture
- Cognitive science
- Cultured neuronal networks
- Memristor
- Neural network software
- Neuro-fuzzy
- Neuroscience
- Parallel distributed processing
- Predictive analytics
- Radial basis function network
- Recurrent neural networks
- Simulated reality
- Support vector machine
- Tensor product network
- Time delay neural network
- 20Q is a neural network implementation of the 20 questions game

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## External links

- International Neural Network Society (INNS) <sup>[25]</sup>
- European Neural Network Society (ENNS) <sup>[26]</sup>
- Japanese Neural Network Society (JNNS) <sup>[27]</sup>
- IEEE Computational Intelligence Society (IEEE CIS) <sup>[28]</sup>
- A Brief Introduction to Neural Networks (D. Kriesel) <sup>[29]</sup> - Illustrated, bilingual manuscript about artificial neural networks; Topics so far: Perceptrons, Backpropagation, Radial Basis Functions, Recurrent Neural Networks, Self Organizing Maps, Hopfield Networks.
- Flood: An open source neural networks C++ library <sup>[30]</sup>
- LearnArtificialNeuralNetworks <sup>[31]</sup> - Robot control and neural networks
- NPatternRecognizer <sup>[32]</sup> - A fast machine learning algorithm library written in C#. It contains SVM, neural networks, Bayes, boost, k-nearest neighbor, decision tree, ..., etc.
- Review of Neural Networks in Materials Science <sup>[33]</sup>
- Artificial Neural Networks Tutorial in three languages (Univ. Polit cnica de Madrid) <sup>[34]</sup>
- Introduction to Neural Networks and Knowledge Modeling <sup>[35]</sup>
- Introduction to Artificial Neural Networks <sup>[36]</sup>
- In Situ Adaptive Tabulation: <sup>[37]</sup> - A neural network alternative.
- Another introduction to ANN <sup>[38]</sup>
- Prediction with neural networks <sup>[39]</sup> - includes Java applet for online experimenting with prediction of a function
- Next Generation of Neural Networks <sup>[40]</sup> - Google Tech Talks
- Perceptual Learning <sup>[41]</sup> - Artificial Perceptual Neural Network used for machine learning to play Chess
- European Centre for Soft Computing <sup>[42]</sup>
- Performance of Neural Networks <sup>[43]</sup>
- Neural Networks and Information <sup>[44]</sup>

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# Theoretical physics

**Theoretical physics** is a branch of physics which employs mathematical models and abstractions of physics in an attempt to explain natural phenomena. Its central core is mathematical physics,<sup>[1]</sup> though other conceptual techniques are also used. The goal is to rationalize, explain and predict physical phenomena. The advancement of science depends in general on the interplay between experimental studies and theory. In some cases, theoretical physics adheres to standards of mathematical rigor while giving little weight to experiments and observations. For example, while developing special relativity, Albert Einstein was concerned with the Lorentz transformation which left Maxwell's equations invariant, but was apparently uninterested in the Michelson-Morley experiment on Earth's drift through a luminiferous ether. On the other hand, Einstein was awarded the Nobel Prize for explaining the photoelectric effect, previously an experimental result lacking a theoretical formulation.

## Overview

A **physical theory** is a model of physical events. It is judged by the extent to which its predictions agree with empirical observations. The quality of a physical theory is also judged on its ability to make new predictions which can be verified by new observations. A physical theory differs from a mathematical theorem in that while both are based on some form of axioms, judgment of mathematical applicability is not based on agreement with any experimental results.

$$\text{Ricci} = k g$$

*The equations for an Einstein manifold, used in general relativity to describe the curvature of spacetime*

A physical theory involves one or more relationships between various measurable quantities. Archimedes realized that a ship floats by displacing its mass of water, Pythagoras understood the relation between the length of a vibrating string and the musical tone it produces, and how to calculate the length of a rectangle's diagonal. Other examples include entropy as a measure of the uncertainty regarding the positions and motions of unseen particles and the quantum mechanical idea that (action and) energy are not continuously variable.

Sometimes the vision provided by pure mathematical systems can provide clues to how a physical system might be modeled; e.g., the notion, due to Riemann and others, that space itself might be curved.

Theoretical advances may consist in setting aside old, incorrect paradigms (e.g., Burning consists of evolving phlogiston, or Astronomical bodies revolve around the Earth) or may be an alternative model that provides answers that are more accurate or that can be more widely applied.

Physical theories become accepted if they are able to make correct predictions and no (or few) incorrect ones. The theory should have, at least as a secondary objective, a certain economy and elegance (compare to mathematical beauty), a notion sometimes called "Occam's razor" after the 13th-century English philosopher William of Occam (or Ockham), in which the simpler of two theories that describe the same matter just as adequately is preferred. (But conceptual simplicity may mean mathematical complexity.) They are also more likely to be accepted if they connect a wide range of phenomena. Testing the consequences of a theory is part of the scientific method.

Physical theories can be grouped into three categories: *mainstream theories*, *proposed theories* and *fringe theories*.

## History

Theoretical physics began at least 2,300 years ago, under the pre-Socratic Greek philosophers, and continued by Plato; and Aristotle, whose views held sway for a millennium. In medieval times, during the rise of the universities, the only acknowledged intellectual disciplines were theology, mathematics, medicine, and law. As the concepts of matter, energy, space, time and causality slowly began to acquire the form we know today, other sciences spun off from the rubric of natural philosophy. During the Middle Ages and Renaissance, the concept of experimental science, the counterpoint to theory, began with scholars such as Ibn al-Haytham and Francis Bacon. The modern era of theory began perhaps with the Copernican paradigm shift in astronomy, soon followed by Johannes Kepler's expressions for planetary orbits, which summarized the meticulous observations of Tycho Brahe.

The great push toward the modern concept of explanation started with Galileo, one of the few physicists who was both a consummate theoretician and a great experimentalist. The analytic geometry and mechanics of Descartes were incorporated into the calculus and mechanics of Isaac Newton, another theoretician/experimentalist of the highest order. Joseph-Louis Lagrange, Leonhard Euler and William Rowan Hamilton would extend the theory of classical mechanics considerably. Each of these individuals picked up the interactive intertwining of mathematics and physics begun two millennia earlier by Pythagoras.

Among the great conceptual achievements of the 19th and 20th centuries were the consolidation of the idea of energy by the inclusion of heat, then electricity and magnetism and light, and finally mass. The laws of thermodynamics, and especially the introduction of the singular concept of entropy began to provide a macroscopic explanation for the properties of matter.

The pillars of modern physics, and perhaps the most revolutionary theories in the history of physics, have been relativity theory and quantum mechanics. Newtonian mechanics was subsumed under special relativity and Newton's gravity was given a kinematic explanation by general relativity. Quantum mechanics led to an understanding of blackbody radiation and of anomalies in the specific heats of solids — and finally to an understanding of the internal structures of atoms and molecules.

All of these achievements depended on the theoretical physics as a moving force both to suggest experiments and to consolidate results — often by ingenious application of existing mathematics, or, as in the case of Descartes and Newton (with Leibniz), by inventing new mathematics. Fourier's studies of heat conduction led to a new branch of mathematics: infinite, orthogonal series.

Modern theoretical physics attempts to unify theories and explain phenomena in further attempts to understand the Universe, from the cosmological to the elementary particle scale. Where experimentation cannot be done, theoretical physics still tries to advance through the use of mathematical models. Some of their most prominent and well thought out advancements in this field include:

### Prominent theoretical physicists

Famous *theoretical physicists* include

- Christiaan Huyghens (1629–1695)
  - Isaac Newton (1643–1727)
  - Leonhard Euler (1707–1783)
  - Joseph Louis Lagrange (1736–1813)
  - Pierre-Simon Laplace (1749–1827)
  - Joseph Fourier (1768–1830)
  - Nicolas Léonard Sadi Carnot (1796–1842)
  - William Rowan Hamilton (1805–1865)
  - Rudolf Clausius (1822–1888)
  - James Clerk Maxwell (1831–1879)
-

- J. Willard Gibbs (1839–1903)
  - Ludwig Boltzmann (1844–1906)
  - Hendrik A. Lorentz (1853–1928)
  - Henri Poincare (1854–1912)
  - Nikola Tesla (1856–1943)
  - Max Planck (1858–1947)
  - Albert Einstein (1879–1955)
  - Emmy Noether (1882–1935)
  - Max Born (1882–1970)
  - Niels Bohr (1885–1962)
  - Erwin Schrödinger (1887–1961)
  - Louis de Broglie (1892–1987)
  - Satyendra Nath Bose (1894–1974)
  - Wolfgang Pauli (1900–1958)
  - Enrico Fermi (1901–1954)
  - Werner Heisenberg (1901–1976)
  - Paul Dirac (1902–1984)
  - Eugene Wigner (1902–1995)
  - Robert Oppenheimer (1904–1967)
  - Sin-Itiro Tomonaga (1906–1979)
  - Hideki Yukawa (1907–1981)
  - John Bardeen (1908–1991)
  - Lev Landau (1908–1967)
  - Anatoly Vlasov (1908–1975)
  - Nikolay Bogolyubov (1909–1992)
  - Subrahmanyam Chandrasekhar (1910–1995)
  - Richard Feynman (1918–1988)
  - Julian Schwinger (1918–1994)
  - Feza Gursey (1921–1992)
  - Chen Ning Yang (1922– )
  - Freeman Dyson (1923– )
  - Gunnar Källén (1926–1968)
  - Abdus Salam (1926–1996)
  - Murray Gell-Mann (1929– )
  - Riazuddin (1930– )
  - Roger Penrose (1931– )
  - George Sudarshan (1931– )
  - Sheldon Glashow (1932– )
  - Steven Weinberg (1933– )
  - C. R. Hagen (1936–)
  - Michael Berry (1941– )
  - Stephen Hawking (1942– )
  - Alexander Polyakov (1945–)
  - Gerardus 't Hooft (1946– )
  - Jacob Bekenstein (1947–)
  - Bertrand Halperin (1950–)
  - Robert Laughlin (1950–)
-

- Edward Witten (1951– )

## Mainstream theories

**Mainstream theories** (sometimes referred to as *central theories*) are the body of knowledge of both factual and scientific views and possess a usual scientific quality of the tests of repeatability, consistency with existing well-established science and experimentation. There do exist mainstream theories that are generally accepted theories based solely upon their effects explaining a wide variety of data, although the detection, explanation and possible composition are subjects of debate.

## Examples

- Black hole thermodynamics
- Classical mechanics
- Condensed matter physics
- Conservation of energy
- Dark Energy
- Dark matter
- Dynamics
- Electromagnetism
- Field theory
- Fluid dynamics
- General relativity
- Molecular modeling
- Particle physics
- Physical cosmology
- Quantum chromodynamics
- Quantum computers
- Quantum electrochemistry
- Quantum electrodynamics
- Quantum field theory
- Quantum information theory
- Quantum mechanics
- Solid mechanics
- Solid state physics or Condensed Matter Physics and the electronic structure of materials
- Special relativity
- Standard Model
- Statistical mechanics
- Thermodynamics

## Proposed theories

The **proposed theories** of physics are usually relatively new theories which deal with the study of physics which include scientific approaches, means for determining the validity of models and new types of reasoning used to arrive at the theory. However, some proposed theories include theories that have been around for decades and have eluded methods of discovery and testing. Proposed theories can include fringe theories in the process of becoming established (and, sometimes, gaining wider acceptance). Proposed theories usually have not been tested.

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## Examples

- Causal Sets
- Dark energy or Einstein's Cosmological Constant
- Einstein-Rosen Bridge
- Emergence
- Grand unification theory
- Loop quantum gravity
- M-theory
- String theory
- Supersymmetry
- Theory of everything

## Fringe theories

**Fringe theories** include any new area of scientific endeavor in the process of becoming established and some proposed theories. It can include speculative sciences. This includes physics fields and physical theories presented in accordance with known evidence, and a body of associated predictions have been made according to that theory.

Some fringe theories go on to become a widely accepted part of physics. Other fringe theories end up being disproven. Some fringe theories are a form of protoscience and others are a form of pseudoscience. The falsification of the original theory sometimes leads to reformulation of the theory.

## Examples

- Dynamic theory of gravity
- Grand unification theory
- Luminiferous aether
- Scalar field theory (pseudoscience)
- Orgone
- Biefeld Brown Electrogravity

## Thought experiments vs real experiments

"Thought" experiments are situations created in ones mind, asking a question akin to "Suppose you are in this situation. Assuming such is true, what would follow?". They are usually created to investigate phenomena that are not readily experienced in every-day situations. Famous examples of such thought experiments are Schrodinger's cat, the EPR thought experiment, simple illustrations of time dilation, and so on. These usually lead to real experiments designed to verify that the conclusion (and therefore the assumptions) of the thought experiments are correct. The EPR thought experiment lead to the Bell inequalities, which were then tested to various degrees of rigor, leading to the acceptance of the current formulation of quantum mechanics and probabilism as a working hypotheses.

## See also

- Experimental physics
- List of theoretical physicists

## Further reading

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## External links

- Timeline of Theoretical Physics <sup>[2]</sup>
- MIT Center for Theoretical Physics <sup>[3]</sup>
- Electronic Journal of Theoretical Physics (EJTP) <sup>[4]</sup>
- How to Become a Theoretical Physicist by a Nobel Laureate <sup>[5]</sup>
- Theory of longitudinal and transversal angular momentums <sup>[6]</sup>

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